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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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# PRIORITY DOCUMENT

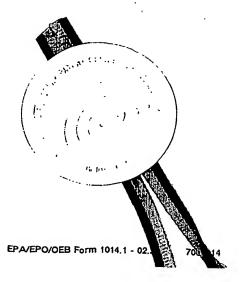
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For the President of the European Patent Office

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R C van Dijk





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Single nucleotide polymorphisms as predictive diagnostics for adverse drug reactions (ADR and drug efficacy)

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# Single Nucleotide Polymorphisms as Predictive Diagnostics for Adverse Drug Reactions (ADR) and Drug Efficacy

### Technical Field

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This invention relates to genetic polymorphisms useful for assessing the response to lipid lowering drug therapy and adverse drug reactions of those medicaments. In addition it relates to genetic polymorphisms useful for assessing cardiovascular risks in humans, including, but not limited to, atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, myocardial infarction, and stroke. Specifically, the present invention identifies and describes gene variations which are individually present in humans with cardiovascular disease states, relative to humans with normal, or non-cardiovascular disease states, and/or in response to medications relevant to cardiovascular disease. Further, the present invention provides methods for the identification and therapeutic use of compounds as treatments of cardiovascular disease or as prophylactic therapy for cardiovascular diseases. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Still further, the present invention provides methods to use gene variations to predict personal medication schemes omitting adverse drug reactions and allowing an adjustment of the drug dose to achieve maximum benefit for the patient. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions.

## Background of the Invention

Cardiovascular disease is a major health risk throughout the industrialized world.

Cardiovascular diseases include but are not limited by the following disorders of the heart and the vascular system: congestive heart failure, myocardial infarction,

atherosclerosis, ischemic diseases of the heart, coronary heart disease, all kinds of atrial and ventricular arrhythmias, hypertensive vascular diseases and peripheral vascular diseases.

Heart failure is defined as a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirement of the metabolizing tissue. It includes all forms of pumping failure such as high-output and low-output, acute and chronic, right-sided or left-sided, systolic or diastolic, independent of the underlying cause.

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Myocardial infarction (MI) is generally caused by an abrupt decrease in coronary blood flow that follows a thrombotic occlusion of a coronary artery previously narrowed by arteriosclerosis. MI prophylaxis (primary and secondary prevention) is included as well as the acute treatment of MI and the prevention of complications.

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Ischemic diseases are conditions in which the coronary flow is restricted resulting in an perfusion which is inadequate to meet the myocardial requirement for oxygen. This group of diseases include stable angina, unstable angina and asymptomatic ischemia.

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Arrhythmias include all forms of atrial and ventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation, atrio-ventricular reentrant tachycardia, preexitation syndrome, ventricular tachycardia, ventricular flutter, ventricular fibrillation) as well as bradycardic forms of arrhythmias.

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Hypertensive vascular diseases include primary as well as all kinds of secondary arterial hypertension (renal, endocrine, neurogenic, others).

Peripheral vascular diseases are defined as vascular diseases in which arterial and/or venous-flow-is-reduced resulting in an imbalance between blood supply and tissue oxygen demand. It includes chronic peripheral arterial occlusive disease (PAOD),

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acute arterial thrombosis and embolism, inflammatory vascular disorders, Raynaud's phenomenon and venous disorders.

Atherosclerosis, the most prevalent of vascular diseases, is the principal cause of heart attack, stroke, and gangrene of the extremities, and thereby the principal cause of death. Atherosclerosis is a complex disease involving many cell types and molecular factors (for a detailed review, see Ross, 1993, Nature 362: 801-809 and Lusis, A. J., Nature 407, 233-241 (2000)). The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions or plaques, preceded and accompanied by inflammation. The advanced lesions of atherosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult. For example, shear stresses are thought to be responsible for the frequent occurrence of atherosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures.

The first observable event in the formation of an atherosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDLs are then taken up in large amounts by the monocytes through scavenger receptors expressed on their surfaces. In contrast to the regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors, the scavenger pathway of uptake is not regulated by the monocytes.

These lipid-filled monocytes are called foam cells, and are the major constituent of the fatty streak. Interactions between foam cells and the endothelial and SMCs which surround them lead to a state of chronic local inflammation which can eventually lead to smooth muscle cell proliferation and migration, and the formation of a fibrous

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plaque. Such plaques occlude the blood vessel concerned and thus restrict the flow of blood, resulting in ischemia.

Ischemia is a condition characterized by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have number of natural causes, including atherosclerotic or restenotic lesions, anemia, or stroke, to name a few. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia may occur in any organ, however, that is suffering a lack of oxygen supply.

The most common cause of ischemia in the heart is atherosclerotic disease of epicardial coronary arteries. By reducing the lumen of these vessels, atherosclerosis causes an absolute decrease in myocardial perfusion in the basal state or limits appropriate increases in perfusion when the demand for flow is augmented. Coronary blood flow can also be limited by arterial thrombi, spasm, and, rarely, coronary emboli, as well as by ostial narrowing due to luctic aortitis. Congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia can also occur if myocardial oxygen demands are abnormally increased, as in severe ventricular hypertrophy due to hypertension or aortic stenosis. The latter can be present with angina that is indistinguishable from that caused by coronary atherosclerosis. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxy-hemoglobin, is a rare cause of myocardial ischemia. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary atherosclerosis.

The foregoing studies are aimed at defining the role of particular gene variations presumed to be involved in the misleading of normal cellular function leading to cardiovascular disease. However, such approaches cannot identify the full panoply of gene variations that are involved in the disease process.

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At present, the only available treatments for cardiovascular disorders are pharmaceutical based medications; that are not targeted to an individual's actual defect; examples include angiotensin converting enzyme (ACE) inhibitors and diuretics for hypertension, insulin supplementation for non-insulin dependent diabetes mellitus (NIDDM), cholesterol reduction strategies for dyslipidaemia, anticoagulants, β blockers for cardiovascular disorders and weight reduction strategies for obesity. If targeted treatment strategies were available it might be possible to predict the response to a particular regime of therapy and could markedly increase the effectiveness of such treatment. Although targeted therapy requires accurate diagnostic tests for disease susceptibility, once these tests are developed the opportunity to utilize targeted therapy will become widespread. Such diagnostic tests could initially serve to identify individuals at most risk of hypertension and could allow them to make changes in lifestyle or diet that would serve as preventative measures. The benefits associated by coupling the diagnostic tests with a system of targeted therapy could include the reduction in dosage of administered drugs and thus the amount of unpleasant side effects suffered by an individual. In more severe cases a diagnostic test may suggest that earlier surgical intervention would be useful in preventing a further deterioration in condition.

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It is an object of the invention to provide genetic diagnosis of predisposition or susceptibility for cardiovascular diseases. Another related object is to provide treatment to reduce or prevent or delay the onset of disease in those predisposed or susceptible to this disease. A further object is to provide means for carrying out this diagnosis.

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Accordingly, a first aspect of the invention provides a method of diagnosis of disease in an individual, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

In another aspect, the invention provides a method of identifying an individual predisposed or susceptible to a disease, said method comprising determining one, various or all genotypes in said individual of the genes listed in the Examples.

The invention is of advantage in that it enables diagnosis of a disease or of certain disease states via genetic analysis which can yield useable results before onset of disease symptoms, or before onset of severe symptoms. The invention is further of advantage in that it enables diagnosis of predisposition or susceptibility to a disease or of certain disease states via genetic analysis.

The invention may also be of use in confirming or corroborating the results of other diagnostic methods. The diagnosis of the invention may thus suitably be used either as an isolated technique or in combination with other methods and apparatus for diagnosis, in which latter case the invention provides a further test on which a diagnosis may be assessed.

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The present invention stems from using allelic association as a method for genotyping individuals; allowing the investigation of the molecular genetic basis for cardiovascular diseases. In a specific embodiment the invention tests for the polymorphisms in the sequences of the listed genes in the Examples. The invention demonstrates a link between this polymorphisms and predispositions to cardiovascular diseases by showing that allele frequencies significantly differ when individuals with "bad" serum lipids are compared to individuals with "good" scrum levels. The meaning of "good and bad" serum lipid levels is defined in Table 1a.

Certain disease states would benefit, that is to say the suffering of the patient may be reduced or prevented or delayed, by administration of treatment or therapy in

advance of disease appearance; this can be more reliably carried out if advance diagnosis of predisposition or susceptibility to disease can be diagnosed.

## Pharmacogenomics and adverse drug reactions

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Adverse drug reactions (ADRs) remain a major clinical problem. A recent metaanalysis suggested that in the USA in 1994, ADRs were responsible for 100 000 deaths, making them between the fourth and sixth commonest cause of death (Lazarou 1998, J. Am. Med. Assoc. 279:1200). Although these figures have been heavily criticized, they emphasize the importance of ADRs. Indeed, there is good evidence that ADRs account for 5% of all hospital admissions and increase the length of stay in hospital by two days at an increased cost of ~\$2500 per patient. ADRs are also one of the commonest causes of drug withdrawal, which has enormous financial implications for the pharmaceutical industry. ADRs, perhaps fortunately, only affect a minority of those taking a particular drug. Although factors that determine susceptibility are unclear in most cases, there is increasing interest in the role of genetic factors. Indeed, the role of inheritable variations in predisposing patients to ADRs has been appreciated since the late 1950s and early 1960s through the discovery of deficiencies in enzymes such as pseudocholinesterase (butyrylcholinesterase) and glucose-6-phosphate dehydrogenase (G6PD). More recently, with the first draft of the human genome just completed, there has been renewed interest in this area with the introduction of terms such as pharmacogenomics and toxicogenomics. Essentially, the aim of pharmacogenomics and pharmacogenetics is to produce personalized medicines, whereby administration of the drug class and dosage is tailored to an individual genotype. Thus, the term pharmacogenetics embraces both efficacy and toxicity.

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. These drugs are effective in reducing the primary and secondary risk of coronary artery disease and coronary events, such

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as heart attack, in middle-aged and older men and women, in both diabetic and nondiabetic patients, and are often prescribed for patients with hyperlipidemia. Statins used in secondary prevention of coronary artery or heart disease significantly reduce the risk of stroke, total mortality and morbidity and attacks of myocardial ischemia; the use of statins is also associated with improvements in endothelial and fibrinolytic functions and decreased platelet thrombus formation.

The tolerability of these drugs during long term administration is an important issue. Adverse reactions involving skeletal muscle are not uncommon, and sometimes serious adverse reactions involving skeletal muscle such as myopathy and rhabdomyolysis may occur, requiring discontinuation of the drug. In addition an increase in serum creatine kinase (CK) may be a sign of a statin related adverse event. The extend of such adverse events can be read from the extend of the CK level increase (as compared to the upper limit of normal [ULN]).

Occasionally arthralgia, alone or in association with myalgia, has been reported. Also an elevation of liver transaminases has been associated with statin administration.

It was shown that the drug response to statin therapy is a class effects, i.e. all known and presumably also all so far undiscovered statins share the same benefical and harmful effects (Ucar, M. et al., Drug Safety 2000, 22:441). It follows that the discovery of diagnostic tools to predict the drug response to a single statin will also be of aid to guide therapy with other statins.

The present invention provides diagnostic tests to predict the patient's individual 25 response to statin therapy. Such responses include, but are not limited by the extent of adverse drug reactions, the level of lipid lowering or the drug's influence on disease states. Those diagnostic tests may predict the response to statin therapy either alone or in combination with another diagnostic test or another drug regimen. 30

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## Detailed Description of the Invention

The present invention is based at least in part on the discovery that a specific allele of a polymorphic region of a so called "candidate gene" (as defined below) is associated with CVD or drug response.

For the present invention the following candidate genes were analyzed:

- Genes found to be expressed in cardiac tissue (Hwang et al., Circulation 1997, 96:4146-4203).
- Genes from the following metabolic pathways and their regulatory elements:

#### Lipid metabolism

Numerous studies have shown a connection between serum lipid levels and cardiovascular diseases. Candidate genes falling into this group include but are not limited by genes of the cholesterol pathway, apolipoproteins and their modifiying factors.

#### 20 Coagulation

Ischemic diseases of the heart and in particular myocardial infarction may be caused by a thrombotic occlusion. Genes falling into this group include all genes of the coagulation cascade and their regulatory elements.

#### Inflammation

Complications of atherosclerosis are the most common causes of death in Western societies. In broad outline atherosclerosis can be considered to be a form of chronic inflammation resulting from interaction modified lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall. This

inflammatory process can ultimately lead to the development of complex lesions, or plaques, that protrude into the arterial lumen. Finally plaque rupture and thrombosis result in the acute clinical complications of myocardial infarction and stroke (Glass et al., Cell 2001, 104:503-516).

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It follows that all genes related to inflammatory processes, including but not limited by cytokines, cytokine receptors and cell adhesion molecules are candidate genes for CVD.

## 10 Glucose and energy metabolism

As glucose and energy metabolism is interdependent with the metabolism of lipids (see above) also the former pathways contain candidate genes. Energy metabolism in general also relates to obesity, which is an independent risk factor for CVD (Melanson et al., Cardiol Rev 2001 9:202-207). In addition high blood glucose levels are associated with many microvascular and macrovascular complications and may therefore affect an individuals disposition to CVD (Duckworth, Curr Atheroscler Rep 2001, 3:383-391).

## 20 Hypertension

As hypertension is an independent risk factor for CVD, also genes that are involved in the regulation of systolic and diastolic blood pressure affect an individuals risk for CVD (Safar, Curr Opin Cardiol 2000, 15:258-263). Interestingly hypertension and diabetes (see above) appear to be interdependent, since hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease. Conversely, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than are normotensive persons (Sowers et al., Hypertension 2001, 37:1053-1059).

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#### Genes related to drug response

Those genes include metabolic pathways involved in the absorption, distribution, metabolism, excretion and toxicity (ADMET) of drugs. Prominent members of this group are the cytochrome P450 proteins which catalyze many reactions involved in drug metabolism.

### Unclassified genes

As stated above, the mechanisms that lead to cardiovascular diseases or define the patient's individual response to drugs are not completely elucidated. Hence also candidate genes were analysed, which could not be assigned to the above listed categories. The present invention is based at least in part on the discovery of polymorphisms, that lie in genomic regions of unknown physiological function.

Results

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After conducting an association study, we surprisingly found polymorphic sites in a number of candidate genes which show a strong correlation with the following phenotypes of the patients analysed: "Healthy" as used herein refers to individuals that neither suffer from existing CVD, nor exhibit an increased risk for CVD through their serum lipid level profile. "CVD prone" as used herein refers to individuals with existing CVD and/or a serum lipid profile that confers a high risk to get CVD (see Table 1a for definitions of healthy and CVD prone serum lipid levels). "High responder" as used herein refers to patients who benefit from relatively small amounts of a given drug. "Low responder" as used herein refers to patients who need relatively high doses in order to obtain benefit from the medication. "Tolerant patient" refers to individuals who can tolerate high doses of a medicament without exhibiting adverse drug reactions. "ADR patient" as used herein refers to individuals who suffer from ADR or show clinical symptoms (like creatine kinase elevation in

blood) even after receiving only minor doses of a medicament (see Table 1b for a detailed definition of drug response phenotypes).

Polymorphic sites in candidate genes that were found to be significantly associated with either of the above mentioned phenotypes will be referred to as "phenotype associated SNPs" (PA SNPs). The respective genomic loci that harbour PA SNPs will be referred to as "phenotype associated genes" (PA genes), irrespective of the actual function of this gene locus.

As PA SNPs are linked to other SNPs in neighboring genes on a chromosome (Linkage Disequilibrium) those SNPs could also be used as marker SNPs. In a recent publication it was shown that SNPs are linked over 100 kb in some cases more than 150 kb (Reich D.E. et al. Nature 411, 199-204, 2001). Hence SNPs lying in regions neighbouring PA SNPs could be linked to the latter and by this being a diagnostic marker. These associations could be performed as described for the gene polymorphism in methods.

### **Definitions**

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For convenience, the meaning of certain terms and phrases employed in the specification, examples, and appended claims are provided below. Moreover, the definitions by itself are intended to explain a further background of the invention.

The term "allele", which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for the gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide, or several nucleotides, and can include substitutions, deletions, and insertions of nucleotides. An allele of a gene can also be a form of a gene containing a mutation.

The term "allelic variant of a polymorphic region of a gene" refers to a region of a gene having one of several nucleotide sequences found in that region of the gene in other individuals.

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"Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present invention.

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The term "a homologue of a nucleic acid" refers to a nucleic acid having a nucleotide sequence having a certain degree of homology with the nucleotide sequence of the nucleic acid or complement thereof. A homologue of a double stranded nucleic acid having SEQ ID NO. X is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with SEQ ID NO. X or with the complement thereof. Preferred homologous of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof.

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The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a hybridization assay.

The term interact is also meant to include "binding" interactions between molecules. Interactions may be, for example, protein-protein, protein-nucleic acid, protein-small molecule or small molecule-nucleic acid in nature.

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The term "intronic sequence" or "intronic nucleotide sequence" refers to the nucleotide sequence of an intron or portion thereof.

The term "isolated" as used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized.

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Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term "isolated" is also used herein to refer to polypeptides which are isolated from other cellular proteins and is meant to encompass both purified and recombinant polypeptides.

The term "lipid" shall refer to a fat or fat-like substance that is insoluble in polar solvents such as water. The term "lipid" is intended to include true fats (e.g. esters of fatty acids and glycerol); lipids (phospholipids, cerebrosides, waxes); sterols (cholesterol, ergosterol) and lipoproteins (e.g. HDL, LDL and VLDL).

The term "locus" refers to a specific position in a chromosome. For example, a locus of a gene refers to the chromosomal position of the gene.

- The term "modulation" as used herein refers to both up-regulation, (i.e., activation or stimulation), for example by agonizing, and down-regulation (i.e. inhibition or suppression), for example by antagonizing of a bioactivity (e.g. expression of a gene).
- The term "molecular-structure" of a gene or a portion thereof refers to the structure as defined by the nucleotide content (including deletions, substitutions, additions of one

or more nucleotides), the nucleotide sequence, the state of methylation, and/or any other modification of the gene or portion thereof.

The term "mutated gene" refers to an allelic form of a gene, which is capable of altering the phenotype of a subject having the mutated gene relative to a subject which does not have the mutated gene. If a subject must be homozygous for this mutation to have an altered phenotype, the mutation is said to be recessive. If one copy of the mutated gene is sufficient to alter the genotype of the subject, the mutation is said to be dominant. If a subject has one copy of the mutated gene and has a phenotype that is intermediate between that of a homozygous and that of a heterozygous (for that gene) subject, the mutation is said to be co-dominant.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, including peptide nucleic acids (PNA), morpholino oligonucleotides (J. Summerton and D. Weller, Antisense and Nucleic Acid Drug Development 7:187 (1997)) and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine. For purposes of clarity, when referring herein to a nucleotide of a nucleic acid, which can be DNA or an RNA, the term "adenosine", "cytidine", "guanosine", and "thymidine" are used. It is understood that if the nucleic acid is RNA, a nucleotide having a uracil base is uridine.

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The term "nucleotide sequence complementary to the nucleotide sequence set forth in SEQ ID NO. x" refers to the nucleotide sequence of the complementary strand of a nucleic acid strand having SEQ ID NO. x. The term "complementary strand" is used herein interchangeably with the term "complement". The complement of a nucleic acid strand can be the complement of a coding strand or the complement of a non-coding strand. When referring to double stranded nucleic acids, the complement of a

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nucleic acid having SEQ ID NO. x refers to the complementary strand of the strand having SEQ ID NO. x or to any nucleic acid having the nucleotide sequence of the complementary strand of SEQ ID NO. x. When referring to a single stranded nucleic acid having the nucleotide sequence SEQ ID NO. x, the complement of this nucleic acid is a nucleic acid having a nucleotide sequence which is complementary to that of SEQ ID NO. x. The nucleotide sequences and complementary sequences thereof are always given in the 5' to 3' direction. The term "complement" and "reverse complement" are used interchangeably herein.

The term "operably linked" is intended to mean that the promoter is associated with the nucleic acid in such a manner as to facilitate transcription of the nucleic acid.

The term "polymorphism" refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a "polymorphic region of a gene". A polymorphic region can be a single nucleotide, the identity of which differs in different alleles. A polymorphic region can also be several nucleotides long.

A "polymorphic gene" refers to a gene having at least one polymorphic region.

To describe a "polymorphic site" in a nucleotide sequence often there is used an "ambiguity code" that stands for the possible variations of nucleotides in one site. The list of ambiguity codes is summarized in the following table:

Ambiguity	Codes
(TUPAC Nomenclature)	
В	c/g/t
.D	. a/g/t
H	a/c/t
K ·	g/t
M	a/c
. N	· a/c/g/t
R	. a/g
S	c/g
V .	a/c/g
W	a/t
Y	c/t

So, for example, a "R" in a nucleotide sequence means that either an "a" or a "g" could be at that position.

The terms "protein", "polypeptide" and "peptide" are used interchangeably herein when referring to a gene product.

A "regulatory element", also termed herein "regulatory sequence is intended to include elements which are capable of modulating transcription from a basic promoter and include elements such as enhancers and silencers. The term "enhancer", also referred to herein as "enhancer element", is intended to include regulatory elements capable of increasing, stimulating, or enhancing transcription from a basic promoter. The term "silencer", also referred to herein as "silencer element" is intended to include regulatory elements capable of decreasing, inhibiting, or repressing transcription from a basic promoter. Regulatory elements are typically present in 5' flanking regions of genes. However, regulatory elements have also been shown to be present in other regions of a gene, in particular in introns. Thus, it is possible that genes have regulatory elements located in introns, exons, coding

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regions, and 3' flanking sequences. Such regulatory elements are also intended to be encompassed by the present invention and can be identified by any of the assays that can be used to identify regulatory elements in 5' flanking regions of genes.

The term "regulatory element" further encompasses "tissue specific" regulatory elements, i.e., regulatory elements which effect expression of the selected DNA sequence preferentially in specific cells (e.g., cells of a specific tissue). gene expression occurs preferentially in a specific cell if expression in this cell type is significantly higher than expression in other cell types. The term "regulatory element" also encompasses non-tissue specific regulatory elements, i.e., regulatory elements which are active in most cell types. Furthermore, a regulatory element can be a constitutive regulatory element, i.e., a regulatory element which constitutively regulates transcription, as opposed to a regulatory element which is inducible, i.e., a regulatory element which is active primarily in response to a stimulus. A stimulus can be, e.g., a molecule, such as a hormone, cytokine, heavy metal, phorbol ester, cyclic AMP (cAMP), or retinoic acid.

Regulatory elements are typically bound by proteins, e.g., transcription factors. The term "transcription factor" is intended to include proteins or modified forms thereof, which interact preferentially with specific nucleic acid sequences, i.e., regulatory elements, and which in appropriate conditions stimulate or repress transcription. Some transcription factors are active when they are in the form of a monomer. Alternatively, other transcription factors are active in the form of a dimer consisting of two identical proteins or different proteins (heterodimer). Modified forms of transcription factors are intended to refer to transcription factors having a post-translational modification, such as the attachment of a phosphate group. The activity of a transcription factor is frequently modulated by a post-translational modification. For example, certain transcription factors are active only if they are phosphorylated on specific residues. Alternatively, transcription factors can be active in the absence of phosphorylated residues and become inactivated by phosphorylation. A list of

known transcription factors and their DNA binding site can be found, e.g., in public databases, e.g., TFMATRIX Transcription Factor Binding Site Profile database.

As used herein, the term "specifically hybridizes" or "specifically detects" refers to the ability of a nucleic acid molecule of the invention to hybridize to at least approximately 6, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 or 140 consecutive nucleotides of either strand of a gene.

The term "wild-type allele" refers to an allele of a gene which, when present in two copies in a subject results in a wild-type phenotype. There can be several different wild-type alleles of a specific gene, since certain nucleotide changes in a gene may not affect the phenotype of a subject having two copies of the gene with the nucleotide changes.

"Adverse drug reaction" (ADR) as used herein refers to an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, whichpredicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. In it's most severe form an ADR might lead to the death of an individual.

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The term "Drug Response" is intended to mean any response that a patient exhibits upon drug administration. Specifically drug response includes beneficial, i.e. desired drug effects, ADR or no detectable reaction at all. More specifically the term drug response could also have a qualitative meaning, i.e. it embraces low or high beneficial effects, respectively and mild or severe ADR, respectively. The term "Statin Response" as used herein refers to drug response after statin administration. An individual drug response includes also a good or bad metabolizing of the drug, meaning that "bad metabolizers" accumulate the drug in the body and by this could show side effects of the drug due to accumulative overdoses.

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"Candidate gene" as used herein includes genes that can be assigned to either normal cardiovascular function or to metabolic pathways that are related to onset and/or progression of cardiovascular diseases.

With regard to drug response the term "candidate gene" includes genes that can be assigned to distinct phenotypes regarding the patient's response to drug administration. Those phenotypes may include patients who benefit from relatively small amounts of a given drug (high responders) or patients who need relatively high doses in order to obtain the same benefit (low responders). In addition those phenotypes may include patients who can tolerate high doses of a medicament without exhibiting ADR, or patients who suffer from ADR even after receiving only low doses of a medicament.

As neither the development of cardiovascular diseases nor the patient's response to drug administration is completely understood, the term "candidate gene" may also comprise genes with presently unknown function.

"PA SNP" (phenotype associated SNP) refers to a polymorphic site which shows a significant association with a patients phenotype (healthy, diseased, low or high responder, drug tolerant, ADR prone, etc.)

"PA gene" (phenotype associated gene) refers to a genomic locus harbouring a PA SNP, irrespective of the actual function of this gene locus.

25 PA gene polypeptide refers to a polypeptide encoded at least in part by a PA gene.

The term "Secondary SNP" is intended to mean a SNP that is in neighborhood to at least one other ("primary") SNP. Due to linkage disequillibrium both primary and secondary SNP(s) might shown a similar association with a phenotype.

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The term "Haplotype" as used herein refers to a group of two or more SNPs that are functionally and/or spatially linked. I.e. haplotypes define groups of SNPs that lie inside genes belonging to identical (or related metabolic) pathways and/or lie on the same chromosome. Haplotypes are expected to give better predictive/diagnostic information than a single SNP

The term "statin" is intended to embrace all inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins specifically inhibit the enzyme HMG-CoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. Known statins are Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin and Simvastatin.

## Methods for Assessing Cardiovascular Status

The present invention provides diagnostic methods for assessing cardiovascular status in a human individual. Cardiovascular status as used herein refers to the physiological status of an individual's cardiovascular system as reflected in one or more markers or indicators. Status markers include without limitation clinical measurements such as, e.g., blood pressure, electrocardiographic profile, and differentiated blood flow analysis as well as measurements of LDL- and HDL-Cholesterol levels, other lipids and other well established clinical parameters that are standard in the art. Status markers according to the invention include diagnoses of one or more cardiovascular syndromes, such as, e.g., hypertension, acute myocardial infarction, silent myocardial infarction, stroke, and atherosclerosis. It will be understood that a diagnosis of a cardiovascular syndrome made by a medical practitioner encompasses clinical measurements and medical judgement. Status markers according to the invention are assessed using conventional methods well known in the art. Also included in the evaluation of cardiovascular status are quantitative or qualitative changes in status markers with time, such as would be used, e.g., in the determination of an individual's response to a particular therapeutic regimen.

The methods are carried out by the steps of:

- (i) determining the sequence of one or more polymorphic positions within one, several or all of the genes listed in Examples or other genes mentioned in this file in the individual to establish a polymorphic pattern for the individual; and
- comparing the polymorphic pattern established in (i) with the polymorphic (ii) patterns of humans exhibiting different markers of cardiovascular status. The 10 polymorphic pattern of the individual is, preferably, highly similar and, most preferably, identical to the polymorphic pattern of individuals who exhibit particular status markers, cardiovascular syndromes, and/or particular patterns of response to therapeutic interventions. Polymorphic patterns may also include polymorphic positions in other genes which are shown, in combination with one or more polymorphic positions in the genes listed in the 15 Examples, to correlate with the presence of particular status markers. In one embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who have been shown to respond positively or negatively to a particular therapeutic regimen. 20 Therapeutic regimen as used herein refers to treatments aimed at the elimination or amelioration of symptoms and events associated cardiovascular disease. Such treatments include without limitation one or more of alteration in diet, lifestyle, and exercise regimen; invasive and noninvasive surgical techniques such as atherectomy, angioplasty, and coronary bypass surgery; 25 and pharmaceutical interventions, such as administration of ACE inhibitors, angiotensin II receptor antagonists, diuretics, alpha-adrenoreceptor antagonists, cardiac glycosides, phosphodiesterase inhibitors, beta-adrenoreceptor antagonists, calcium channel blockers, HMG-CoA reductase inhibitors, imidazoline receptor blockers, endothelin receptor blockers, organic nitrites, 30and modulators of protein function of genes listed in the Examples. Interventions with pharmaceutical agents not yet known whose activity

correlates with particular polymorphic patterns associated with cardiovascular disease are also encompassed. It is contemplated, for example, that patients who are candidates for a particular therapeutic regimen will be screened for polymorphic patterns that correlate with responsivity to that particular regimen.

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In a preferred embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more markers of cardiovascular disease, such as, e.g., elevated LDL-Cholesterol levels, high blood pressure, abnormal electrocardiographic profile, myocardial infarction, stroke, or atherosclerosis.

In another embodiment, the method involves comparing an individual's polymorphic pattern with polymorphic patterns of individuals who exhibit or have exhibited one or more drug related phenotypes, such as, e.g., low or high drug response, or adverse drug reactions.

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In practicing the methods of the invention, an individual's polymorphic pattern can be established by obtaining DNA from the individual and determining the sequence at predetermined polymorphic positions in the genes such as those described in this file.

The DNA may be obtained from any cell source. Non-limiting examples of cell sources available in clinical practice include blood cells, buccal cells, cervicovaginal cells, epithelial cells from urine, fetal cells, or any cells present in tissue obtained by biopsy. Cells may also be obtained from body fluids, including without limitation blood, saliva, sweat, urine, cerebrospinal fluid, feces, and tissue exudates at the site of infection or inflammation. DNA is extracted from the cell source or body fluid using any of the numerous methods that are standard in the art. It will be understood that the particular method used to extract DNA will depend on the nature of the source.

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## Diagnostic and Prognostic Assays

The present invention provides methods for determining the molecular structure of at least one polymorphic region of a gene, specific allelic variants of said polymorphic region being associated with cardiovascular disease. In one embodiment, determining the molecular structure of a polymorphic region of a gene comprises determining the identity of the allelic variant. A polymorphic region of a gene, of which specific alleles are associated with cardiovascular disease can be located in an exon, an intron, at an intron/exon border, or in the promoter of the gene.

The invention provides methods for determining whether a subject has, or is at risk, of developing a cardiovascular disease. Such disorders can be associated with an aberrant gene activity, e.g., abnormal binding to a form of a lipid, or an aberrant gene protein level. An aberrant gene protein level can result from an aberrant transcription or post-transcriptional regulation. Thus, allelic differences in specific regions of a gene can result in differences of gene protein due to differences in regulation of expression. In particular, some of the identified polymorphisms in the human gene may be associated with differences in the level of transcription, RNA maturation, splicing, or translation of the gene or transcription product.

In preferred embodiments, the methods of the invention can be characterized as comprising detecting, in a sample of cells from the subject, the presence or absence of a specific allelic variant of one or more polymorphic regions of a gene. The allelic differences can be: (i) a difference in the identity of at least one nucleotide or (ii) a difference in the number of nucleotides, which difference can be a single nucleotide or several nucleotides.

A preferred detection method is allele specific hybridization using probes overlapping the polymorphic-site-and-having-about-5, 10, 20, 25, or 30 nucleotides around the polymorphic region. Examples of probes for detecting specific allelic

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variants of the polymorphic region located in intron X are probes comprising a nucleotide sequence set forth in any of SEQ ID NO. X. In a preferred embodiment of the invention, several probes capable of hybridizing specifically to allelic variants are attached to a solid phase support, e.g., a "chip". Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. For example a chip can hold up to 250,000 oligonucleotides (GeneChip, Affymetrix). Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (1996) Human Mutation 7:244 and in Kozal et al. (1996) Nature Medicine 2:753. In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test nucleic acid and hybridization to the specific probes is detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment. For example, the identity of the allelic variant of the nucleotide polymorphism of nucleotide A or G at position 33 of Seq ID 1 (baySNP179) and that of other possible polymorphic regions can be determined in a single hybridization experiment.

In other detection methods, it is necessary to first amplify at least a portion of a gene prior to identifying the allelic variant. Amplification can be performed, e.g., by PCR and/or LCR, according to methods known in the art. In one embodiment, genomic DNA of a cell is exposed to two PCR primers and amplification for a number of cycles sufficient to produce the required amount of amplified DNA. In preferred embodiments, the primers are located between 40 and 350 base pairs apart. Preferred primers for amplifying gene fragments of genes of this file are listed in Table 2 in the Examples.

(Guatelli, J. C. et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:1874-1878), transcriptional amplification system (Kwoh, D. Y. et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:1173-1177), Q-Beta Replicase (Lizardi, P. M. et al., 1988, Bio/Technology 6:1197), or any other nucleic acid amplification method, followed

by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In one embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence at least a portion of a gene and detect allelic variants, e.g., mutations, by comparing the sequence of the sample sequence with the corresponding wild-type (control) sequence. Exemplary sequencing reactions include those based on techniques developed by Maxam and Gilbert (Proc. Natl Acad Sci. USA (1977) 74:560) or Sanger (Sanger et al (1977) Proc. Nat. Acad. Sci 74:5463). It is also contemplated that any of a variety of automated sequencing procedures may be utilized when performing the subject assays (Biotechniques (1995) 19:448), including sequencing by mass spectrometry (see, for example, U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/16101, entitled DNA Sequencing by Mass Spectrometry by H. Koster; U.S. Pat. No. 5,547,835 and international patent application Publication Number WO 94/21822 entitled "DNA Sequencing by Mass Spectrometry Via Exonuclease Degradation" by H. Koster), and U.S. Pat. No. 5,605,798 and International Patent Application No. PCT/US96/03651 entitled DNA Diagnostics Based on Mass Spectrometry by H. Koster; Cohen et al. (1996) Adv Chromatogr 36:127-162; and Griffin et al. (1993) Appl Biochem Biotechnol 38:147-159). It will be evident to one skilled in the art that, for certain embodiments, the occurrence of only one, two or three of the nucleic acid bases need be determined in the sequencing reaction. For instance, A-track or the like, e.g., where only one nucleotide is detected, can be carried out.

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Yet other sequencing methods are disclosed, e.g., in U.S. Pat. No. 5,580,732 entitled "Method of DNA sequencing employing a mixed DNA-polymer chain probe" and U.S. Pat. No. 5,571,676 entitled "Method for mismatch-directed in vitro DNA sequencing".

In some cases, the presence of a specific allele of a gene in DNA from a subject can be shown by restriction enzyme analysis. For example, a specific nucleotide polymorphism can result in a nucleotide sequence comprising a restriction site which is absent from the nucleotide sequence of another allelic variant.

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In other embodiments, alterations in electrophoretic mobility is used to identify the type of gene allelic variant. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) Proc Natl. Acad. Sci USA 86:2766, see also Cotton (1993) Mutat Res 285:125-144; and Hayashi (1992) Genet Anal Tech Appl 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids are denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In another preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) Trends Genet 7:5).

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In yet another embodiment, the identity of an allelic variant of a polymorphic region is obtained by analyzing the movement of a nucleic acid comprising the polymorphic region in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al (1985) Nature 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing agent gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys Chem 265:1275).

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Examples of techniques for detecting differences of at least one nucleotide between 2 nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes may be prepared in which the known polymorphic nucleotide is placed centrally (allele-specific probes) and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) Nature 324:163); Saiki et al (1989) Proc. Natl Acad. Sci USA 86:6230; and Wallace et al. (1979) Nucl. Acids Res. 6:3543). Such allele specific oligonucleotide hybridization techniques may be used for the simultaneous detection of several nucleotide changes in different polymorphic regions of gene. For example, oligonucleotides having nucleotide sequences of specific allelic variants are attached to a hybridizing membrane and this membrane is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal will then reveal the identity of the nucleotides of the sample nucleic acid.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used. Oligonucleotides used as primers for specific amplification may carry the allelic variant of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al (1989) Nucleic Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) Tibtech 11:238; Newton et al. (1989) Nucl. Acids Res. 17:2503). This technique is also termed "PROBE" for Probe Oligo Base Extension. In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al (1992) Mol. Cell Probes 6:1).

In another embodiment, identification of the allelic variant is carried out using an oligonucleotide ligation assay (OLA), as described, e.g., in U.S. Pat. No. 4,998,617 and in Landegren, U. et al., Science-241:1077-1080-(1988). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting

sequences of a single strand of a target. One of the oligonucleotides is linked to a separation marker, e.g., biotinylated, and the other is detectably labeled. If the precise complementary sequence is found in a target molecule, the oligonucleotides will hybridize such that their termini abut, and create a ligation substrate. Ligation then permits the labeled oligonucleotide to be recovered using avidin, or another biotin ligand. Nickerson, D. A. et al. have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D. A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 87:8923-8927 (1990). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA.

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Several techniques based on this OLA method have been developed and can be used to detect specific allelic variants of a polymorphic region of a gene. For example, U.S. Pat. No. 5,593,826 discloses an OLA using an oligonucleotide having 3'-amino group and a 5'-phosphorylated oligonucleotide to form a conjugate having a phosphoramidate linkage. In another variation of OLA described in Tobe et al. ((1996)Nucleic Acids Res 24: 3728), OLA combined with PCR permits typing of two alleles in a single microtiter well. By marking each of the allele-specific primers with a unique hapten, i.e. digoxigenin and fluorescein, each LA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

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The invention further provides methods for detecting single nucleotide polymorphisms in a gene. Because single nucleotide polymorphisms constitute sites of variation flanked by regions of invariant sequence, their analysis requires no more than the determination of the identity of the single nucleotide present at the site of variation and it is unnecessary to determine a complete gene sequence for each patient. Several methods have been developed to facilitate the analysis of such single nucleotide polymorphisms.

In one embodiment, the single base polymorphism can be detected by using a specialized exonuclease-resistant nucleotide, as disclosed, e.g., in Mundy, C. R. (U.S. Pat. No. 4,656,127). According to the method, a primer complementary to the allelic sequence immediately 3' to the polymorphic site is permitted to hybridize to a target molecule obtained from a particular animal or human. If the polymorphic site on the target molecule contains a nucleotide that is complementary to the particular exonuclease-resistant nucleotide derivative present, then that derivative will be incorporated onto the end of the hybridized primer. Such incorporation renders the primer resistant to exonuclease, and thereby permits its detection. Since the identity of the exonuclease-resistant derivative of the sample is known, a finding that the primer has become resistant to exonucleases reveals that the nucleotide present in the polymorphic site of the target molecule was complementary to that of the nucleotide derivative used in the reaction. This method has the advantage that it does not require the determination of large amounts of extraneous sequence data.

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In another embodiment of the invention, a solution-based method is used for determining the identity of the nucleotide of a polymorphic site. Cohen, D. et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087). As in the Mundy method of U.S. Pat. No. 4,656,127, a primer is employed that is complementary to allelic sequences immediately 3' to a polymorphic site. The method determines the identity of the nucleotide of that site using labeled dideoxynucleotide derivatives, which, if complementary to the nucleotide of the polymorphic site will become incorporated onto the terminus of the primer.

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An alternative method, known as Genetic Bit Analysis or GBA TM is described by Goelet, P. et al. (PCT Appln. No. 92/15712). The method of Goelet, P. et al. uses mixtures of labeled terminators and a primer that is complementary to the sequence 3' to a polymorphic site. The labeled terminator that is incorporated is thus determined by, and complementary to, the nucleotide present in the polymorphic site of-the-target molecule being evaluated. In contrast to the method of Cohen et al. (French Patent 2,650,840; PCT Appln. No. WO91/02087) the method of Goelet, P. et

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al. is preferably a heterogeneous phase assay, in which the primer or the target molecule is immobilized to a solid phase.

Recently, several primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., Nucl. Acids. Res. 17:7779-7784 (1989); Sokolov, B. P., Nucl. Acids Res. 18:3671 (1990); Syvanen, A. -C., et al., Genomics 8:684-692 (1990), Kuppuswamy, M. N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 88:1143-1147 (1991); Prezant, T. R. et al., Hum. Mutat. 1:159-164 (1992); Ugozzoli, L. et al., GATA 9:107-112 (1992); Nyren, P. et al., Anal. Biochem. 208:171-175 (1993)). These methods differ from GBA TM in that they all rely on the incorporation of labeled deoxynucleotides to discriminate between bases at a polymorphic site. In such a format, since the signal is proportional to the number of deoxynucleotides incorporated, polymorphisms that occur in runs of the same nucleotide can result in signals that are proportional to the length of the run (Syvanen, A.-C., et al., Amer. J. Hum. Genet. 52:46-59 (1993)).

For determining the identity of the allelic variant of a polymorphic region located in the coding region of a gene, yet other methods than those described above can be used. For example, identification of an allelic variant which encodes a mutated gene protein can be performed by using an antibody specifically recognizing the mutant protein in, e.g., immunohistochemistry or immunoprecipitation. Antibodies to wild-type gene protein are described, e.g., in Acton et al. (1999) Science 271:518 (antimouse gene antibody cross-reactive with human gene). Other antibodies to wild-type gene or mutated forms of gene proteins can be prepared according to methods known in the art. Alternatively, one can also measure an activity of an gene protein, such as binding to a lipid or lipoprotein. Binding assays are known in the art and involve, s.g., obtaining cells from a subject, and performing binding experiments with a labeled lipid, to determine whether binding to the mutated form of the receptor differs from binding to the wild-type of the receptor.

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If a polymorphic region is located in an exon, either in a coding or non-coding region of the gene, the identity of the allelic variant can be determined by determining the molecular structure of the mRNA, pre-mRNA, or cDNA. The molecular structure can be determined using any of the above described methods for determining the molecular structure of the genomic DNA, e.g., sequencing and SSCP.

The methods described herein may be performed, for example, by utilizing prepackaged diagnostic kits, such as those described above, comprising at least one probe or primer nucleic acid described herein, which may be conveniently used, e.g., to determine whether a subject has or is at risk of developing a disease associated with a specific gene allelic variant.

Sample nucleic acid for using in the above-described diagnostic and prognostic methods can be obtained from any cell type or tissue of a subject. For example, a subject's bodily fluid (e.g. blood) can be obtained by known techniques (e.g. venipuncture) or from human tissues like heart (biopsies, transplanted organs). Alternatively, nucleic acid tests can be performed on dry samples (e.g. hair or skin). Fetal nucleic acid samples for prenatal diagnostics can be obtained from maternal blood as described in International Patent Application No.WO91/07660 to Bianchi. Alternatively, amniocytes or chorionic villi may be obtained for performing prenatal testing.

Diagnostic procedures may also be performed in situ directly upon tissue sections (fixed and/or frozen) of patient tissue obtained from biopsies or resections, such that no nucleic acid purification is necessary. Nucleic acid reagents may be used as probes and/or primers for such in situ procedures (see, for example, Nuovo, G. J., 1992, PCR in situ hybridization: protocols and applications, Raven Press, New York).

In addition to methods which focus primarily on the detection of one nucleic acidsequence, profiles may also be assessed in such detection schemes. Fingerprint profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

In practicing the present invention, the distribution of polymorphic patterns in a large number of individuals exhibiting particular markers of cardiovascular status or drug response is determined by any of the methods described above, and compared with the distribution of polymorphic patterns in patients that have been matched for age, ethnic origin, and/or any other statistically or medically relevant parameters, who exhibit quantitatively or qualitatively different status markers. Correlations are achieved using any method known in the art, including nominal logistic regression, chi square tests or standard least squares regression analysis. In this manner, it is possible to establish statistically significant correlations between particular polymorphic patterns and particular cardiovascular statuses (given in p values). It is further possible to establish statistically significant correlations between particular polymorphic patterns and changes in cardiovascular status or drug response such as, would result, e.g., from particular treatment regimens. In this manner, it is possible to correlate polymorphic patterns with responsivity to particular treatments.

In another embodiment of the present invention two or more polymorphic regions are combined to define so called 'haplotypes'. Haplotypes are groups of two or more SNPs that are functionally and/or spatially linked. It is possible to combine SNPs that are disclosed in the present invention either with each other or with additional polymorphic regions to form a haplotype. Haplotypes are expected to give better predictive/diagnostic information than a single SNP.

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In a preferred embodiment of the present invention a panel of SNPs/haplotypes is defined that predicts the risk for CVD or drug response. This predictive panel is then used for genotyping of patients on a platform that can genotype multiple SNPs at the same time (Multiplexing). Preferred platforms are e.g. gene chips (Affymetrix) or the Luminex LabMAP reader. The subsequent identification and evaluation of a patient's haplotype can then help to guide specific and individualized therapy.

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For example the present invention can identify patients exhibiting genetic polymorphisms or haplotypes which indicate an increased risk for adverse drug reactions. In that case the drug dose should be lowered in a way that the risk for ADR is diminished. Also if the patient's response to drug administration is particularly high (or the patient is badly metabolizing the drug), the drug dose should be lowered to avoid the risk of ADR.

In turn if the patient's response to drug administration is low (or the patient is a particularly high metabolizer of the drug), and there is no evident risk of ADR, the drug dose should be raised to an efficacious level.

It is self evident that the ability to predict a patient's individual drug response should affect the formulation of a drug, i.e. drug formulations should be tailored in a way that they suit the different patient classes (low/high responder, poor/good metabolizer, ADR prone patients). Those different drug formulations may encompass different doses of the drug, i.e. the medicinal products contains low or high amounts of the active substance. In another embodiement of the invention the drug formulation may contain additional substances that facilitate the beneficial effects and/or diminish the risk for ADR (Folkers et al. 1991, US Pat. 5,316,765).

## Isolated Polymorphic Nucleic Acids, Probes, and Vectors

The present invention provides isolated nucleic acids comprising the polymorphic positions described herein for human genes; vectors comprising the nucleic acids; and transformed host cells comprising the vectors. The invention also provides probes which are useful for detecting these polymorphisms.

In practicing the present invention, many conventional techniques in molecular biology, microbiology, and recombinant DNA, are used. Such techniques are well known and are explained fully in, for example, Sambrook et al., 1989, Molecular

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Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; DNA Cloning: A Practical Approach, Volumes I and II, 1985 (D. N. Glover ed.); Oligonucleotide Synthesis, 1984, (M. L.Gait ed.); Nucleic Acid Hybridization, 1985, (Hames and Higgins); Ausubel et al., Current Protocols in Molecular Biology, 1997, (John Wiley and Sons); and Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively).

Insertion of nucleic acids (typically DNAs) comprising the sequences in a functional surrounding like full length cDNA of the present invention into a vector is easily accomplished when the termini of both the DNAs and the vector comprise compatible restriction sites. If this cannot be done, it may be necessary to modify the termini of the DNAs and/or vector by digesting back single-stranded DNA overhangs generated by restriction endonuclease cleavage to produce blunt ends, or to achieve the same result by filling in the single-stranded termini with an appropriate DNA polymerase.

Alternatively, any site desired may be produced, e.g., by ligating nucleotide sequences (linkers) onto the termini. Such linkers may comprise specific oligonucleotide sequences that define desired restriction sites. Restriction sites can also be generated by the use of the polymerase chain reaction (PCR). See, e.g., Saiki et al., 1988, Science 239:48. The cleaved vector and the DNA fragments may also be modified if required by homopolymeric tailing.

The nucleic acids may be isolated directly from cells or may be chemically synthesized using known methods. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either chemically synthesized strands or genomic material as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can further be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression.

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The nucleic acids of the present invention may be flanked by native gene sequences, or may be associated with heterologous sequences, including promoters, enhancers, response elements, signal sequences, polyadenylation sequences, introns, 5'- and 3'noncoding regions, and the like. The nucleic acids may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphoroamidates, carbamates, morpholines etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.). Nucleic acids may contain one or more additional covalently linked moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), intercalators (e.g., acridine, psoralen, etc.), chelators (e.g., metals, radioactive metals, iron, oxidative metals, etc.), and alkylators. PNAs are also included. The nucleic acid may be derivatized by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the nucleic acid sequences of the present invention may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

The invention also provides nucleic acid vectors comprising the gene sequences or derivatives or fragments thereof of genes described in the Examles. A large number of vectors, including plasmid and fungal vectors, have been described for replication and/or expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple cloning or protein expression. Non-limiting examples of suitable vectors include without limitation pUC plasmids, pET plasmids (Novagen, Inc., Madison, Wis.), or pRSET or pREP (Invitrogen, San Diego, Calif.), and many appropriate host cells, using methods disclosed or cited herein or otherwise known to those skilled in the relevant art. The particular choice of vector/host is not critical to the practice of the invention.

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Suitable host cells may be transformed/transfected/infected as appropriate by any suitable method including electroporation, CaCl2 mediated DNA uptake, fungal or viral infection, microinjection, microprojectile, or other established methods. Appropriate host cells included bacteria, archebacteria, fungi, especially yeast, and plant and animal cells, especially mammalian cells. A large number of transcription initiation and termination regulatory regions have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Examples of these regions, methods of isolation, manner of manipulation, etc. are known in the art. Under appropriate expression conditions, host cells can be used as a source of recombinantly produced peptides and polypeptides encoded by genes of the Examples. Nucleic acids encoding peptides or polypeptides from gene sequences of the Examples may also be introduced into cells by recombination events. For example, such a sequence can be introduced into a cell and thereby effect homologous recombination at the site of an endogenous gene or a sequence with substantial identity to the gene. Other recombination-based methods such as nonhomologous recombinations or deletion of endogenous genes by homologous recombination may also be used.

In case of proteins that form heterodimers or other multimers, both or all subunits have to be expressed in one system or cell.

The nucleic acids of the present invention find use as probes for the detection of genetic polymorphisms and as templates for the recombinant production of normal or variant peptides or polypeptides encoded by genes listed in the Examples.

Probes in accordance with the present invention comprise without limitation isolated nucleic acids of about 10-100 bp, preferably 15-75 bp and most preferably 17-25 bp in length, which hybridize at high stringency to one or more of the polymorphic sequences disclosed herein or to a sequence immediately adjacent to a polymorphic position. Furthermore, in some embodiments a full-length gene sequence may be

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used as a probe. In one series of embodiments, the probes span the polymorphic positions in genes disclosed herein. In another series of embodiments, the probes correspond to sequences immediately adjacent to the polymorphic positions.

# 5 Polymorphic Polypeptides and Polymorphism-Specific Antibodies

The present invention encompasses isolated peptides and polypeptides encoded by genes listed in the Examples comprising polymorphic positions disclosed herein. In one preferred embodiment, the peptides and polypeptides are useful screening targets to identify cardiovascular drugs. In another preferred embodiments, the peptides and polypeptides are capable of eliciting antibodies in a suitable host animal that react specifically with a polypeptide comprising the polymorphic position and distinguish it from other polypeptides having a different sequence at that position.

Polypeptides according to the invention are preferably at least five or more residues in length, preferably at least fifteen residues. Methods for obtaining these polypeptides are described below. Many conventional techniques in protein biochemistry and immunology are used. Such techniques are well known and are explained in Immunochemical Methods in Cell and Molecular Biology, 1987 (Mayer and Waler, eds; Academic Press, London); Scopes, 1987, Protein Purification: Principles and Practice, Second Edition (Springer-Verlag, N.Y.) and Handbook of Experimental Immunology, 1986, Volumes I-IV (Weir and Blackwell eds.).

Nucleic acids comprising protein-coding sequences can be used to direct the ITT recombinant expression of polypeptides encoded by genes disclosed herein in intact cells or in cell-free translation systems. The known genetic code, tailored if desired for more efficient expression in a given host organism, can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The polypeptides may be isolated from human cells, or from heterologous organisms or cells (including, but not limited to, bacteria, fungi, insect, plant, and mammalian cells) into which an

appropriate protein-coding sequence has been introduced and expressed. Furthermore, the polypeptides may be part of recombinant fusion proteins.

Peptides and polypeptides may be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. The polypeptides are preferably prepared by solid phase peptide synthesis as described by Merrifield, 1963, J. Am. Chem. Soc. 85:2149.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. For some purposes, it is preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence. The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against peptides encoded by genes disclosed herein, can be used as purification reagents. Other purification methods are possible.

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The present invention also encompasses derivatives and homologues of the polypeptides. For some purposes, nucleic acid sequences encoding the peptides may be altered by substitutions, additions, or deletions that provide for functionally equivalent molecules, i.e., function-conservative variants. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of similar properties, such as, for example, positively charged amino acids (arginine, lysine, and histidine); negatively charged amino acids (aspartate and glutamate); polar neutral amino acids; and non-polar amino acids.

The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with

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a label capable of providing a detectable signal, either directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

The present invention also encompasses antibodies that specifically recognize the polymorphic positions of the invention and distinguish a peptide or polypeptide containing a particular polymorphism from one that contains a different sequence at that position. Such polymorphic position-specific antibodies according to the present invention include polyclonal and monoclonal antibodies. The antibodies may be elicited in an animal host by immunization with peptides encoded by genes disclosed herein or may be formed by in vitro immunization of immune cells. The immunogenic components used to elicit the antibodies may be isolated from human cells or produced in recombinant systems. The antibodies may also be produced in recombinant systems programmed with appropriate antibody-encoding DNA. Alternatively, the antibodies may be constructed by biochemical reconstitution of purified heavy and light chains. The antibodies include hybrid antibodies (i.e., containing two sets of heavy chain/light chain combinations, each of which recognizes a different antigen), chimeric antibodies (i.e., in which either the heavy chains, light chains, or both, are fusion proteins), and univalent antibodies (i.e., comprised of a heavy chain/light chain complex bound to the constant region of a second heavy chain). Also included are Fab fragments, including Fab' and F(ab).sub.2 fragments of antibodies. Methods for the production of all of the above types of antibodies and derivatives are well-known in the art and are discussed in more detail below. For example, techniques for producing and processing polyclonal antisera are disclosed in Mayer and Walker, 1987, Immunochemical Methods in Cell and Molecular Biology, (Academic Press, London). The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibodyproducing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., Schreier et al., 1980, Hybridoma Techniques; U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies produced against peptides encoded

by genes disclosed herein can be screened for various properties; i.e. for isotype, epitope affinity, etc.

The antibodies of this invention can be purified by standard methods, including but not limited to preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. Purification methods for antibodies are disclosed, e.g., in The Art of Antibody Purification, 1989, Amicon Division, W. R. Grace & Co. General protein purification methods are described in Protein Purification: Principles and Practice, R. K. Scopes, Ed., 1987, Springer-Verlag, New York, N.Y.

Methods for determining the immunogenic capability of the disclosed sequences and the characteristics of the resulting sequence-specific antibodies and immune cells are well-known in the art. For example, antibodies elicited in response to a peptide comprising a particular polymorphic sequence can be tested for their ability to specifically recognize that polymorphic sequence, i.e., to bind differentially to a peptide or polypeptide comprising the polymorphic sequence and thus distinguish it from a similar peptide or polypeptide containing a different sequence at the same position.

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### Kits

As set forth herein, the invention provides diagnostic methods, e.g., for determining the identity of the allelic variants of polymorphic regions present in the gene loci of genes disclosed herein, wherein specific allelic variants of the polymorphic region are associated with cardiovascular diseases. In a preferred embodiment, the diagnostic kit can be used to determine whether a subject is at risk of developing a cardiovascular disease. This information could then be used, e.g., to optimize treatment of such individuals.

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In preferred embodiments, the kit comprises a probe or primer which is capable of hybridizing to a gene and thereby identifying whether the gene contains an allelic variant of a polymorphic region which is associated with a risk for cardiovascular disease. The kit preferably further comprises instructions for use in diagnosing a subject as having, or having a predisposition, towards developing a cardiovascular disease. The probe or primers of the kit can be any of the probes or primers described in this file.

Preferred kits for amplifying a region of a gene comprising a polymorphic region of interest comprise one, two or more primers.

# Autibody-based diagnostic methods and kits:

The invention also provides antibody-based methods for detecting polymorphic patterns in a biological sample. The methods comprise the steps of: (i) contacting a sample with one or more antibody preparations, wherein each of the antibody preparations is specific for a particular polymorphic form of the proteins encoded by genes disclosed herein, under conditions in which a stable antigen-antibody complex can form between the antibody and antigenic components in the sample; and (ii) detecting any antigen-antibody complex formed in step (i) using any suitable means known in the art, wherein the detection of a complex indicates the presence of the particular polymorphic form in the sample.

Typically, immunoassays use either a labelled antibody or a labelled antigenic component (e.g., that competes with the antigen in the sample for binding to the antibody). Suitable labels include without limitation enzyme-based, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays that amplify the signals from the probe are also known, such as, for example, those that utilize biotin and avidin, and enzyme-labelled immunoassays, such as ELISA assays.

The present invention also provides kits suitable for antibody-based diagnostic applications. Diagnostic kits typically include one or more of the following components:

- Polymorphism-specific antibodies. The antibodies may be pre-labelled; alternatively, the antibody may be unlabelled and the ingredients for labelling may be included in the kit in separate containers, or a secondary, labelled antibody is provided; and
- 10 (ii) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.
- The kits referred to above may include instructions for conducting the test.

  Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

# **Drug Targets and Screening Methods**

According to the present invention, nucleotide sequences derived from genes disclosed herein and peptide sequences encoded by genes disclosed herein, particularly those that contain one or more polymorphic sequences, comprise useful targets to identify cardiovascular drugs, i.e., compounds that are effective in treating one or more clinical symptoms of cardiovascular disease. Furthermore, especially when a protein is a multimeric protein that are build of two or more subunits, is a combination of different polymorphic subunits very useful.

Drug targets include without limitation (i) isolated nucleic acids derived from the genes disclosed herein, and (ii) isolated peptides and polypeptides encoded by genes disclosed herein, each of which comprises one or more polymorphic positions.

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# In vitro screening methods:

In one series of embodiments, an isolated nucleic acid comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The methods comprise:

- (i) providing a first nucleic acid containing a particular sequence at a polymorphic position and a second nucleic acid whose sequence is identical to that of the first nucleic acid except for a different sequence at the same polymorphic position;
- (ii) contacting the nucleic acids with a multiplicity of test compounds under conditions appropriate for binding; and
- 15 (iii) identifying those compounds that bind selectively to either the first or second nucleic acid sequence.

Selective binding as used herein refers to any measurable difference in any parameter of binding, such as, e.g., binding affinity, binding capacity, etc.

In another series of embodiments, an isolated peptide or polypeptide comprising one or more polymorphic positions is tested in vitro for its ability to bind test compounds in a sequence-specific manner. The screening methods involve:

- 25 (i) providing a first peptide or polypeptide containing a particular sequence at a polymorphic position and a second peptide or polypeptide whose sequence is identical to the first peptide or polypeptide except for a different sequence at the same polymorphic position;
- 30 (ii) contacting\_the\_polypeptides\_with\_a\_multiplicity\_of\_test\_compounds\_under conditions appropriate for binding; and

- (iii) identifying those compounds that bind selectively to one of the nucleic acid sequences.
- In preferred embodiments, high-throughput screening protocols are used to survey a large number of test compounds for their ability to bind the genes or peptides disclosed above in a sequence-specific manner.

Test compounds are screened from large libraries of synthetic or natural compounds. Numerous means are currently used for random and directed synthesis of saccharide, peptide, and nucleic acid based compounds. Synthetic compound libraries are commercially available from Maybridge Chemical Co. (Trevillet, Cornwall, UK), Comgenex (Princeton, N.J.), Brandon Associates (Merrimack, N.H.), and Microsource (New Milford, Conn.). A rare chemical library is available from Aldrich (Milwaukee, Wis.). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available from e.g. Pan Laboratories (Bothell, Wash.) or MycoSearch (N.C.), or are readily producible. Additionally, natural and synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means.

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### In vivo screening methods

Intact cells or whole animals expressing polymorphic variants of genes disclosed herein can be used in screening methods to identify candidate cardiovascular drugs.

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In one series of embodiments, a permanent cell line is established from an individual exhibiting a particular polymorphic pattern. Alternatively, cells (including without limitation mammalian, insect, yeast, or bacterial cells) are programmed to express a gene comprising one or more polymorphic sequences by introduction of appropriate DNA. Identification of candidate compounds can be achieved using any suitable assay, including without limitation (i) assays that measure selective binding of test

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compounds to particular polymorphic variants of proteins encoded by genes disclosed herein; (ii) assays that measure the ability of a test compound to modify (i.e., inhibit or enhance) a measurable activity or function of proteins encoded by genes disclosed herein; and (iii) assays that measure the ability of a compound to modify (i.e., inhibit or enhance) the transcriptional activity of sequences derived from the promoter (i.e., regulatory) regions of genes disclosed herein.

In another series of embodiments, transgenic animals are created in which (i) one or more human genes disclosed herein, having different sequences at particular polymorphic positions are stably inserted into the genome of the transgenic animal; and/or (ii) the endogenous genes disclosed herein are inactivated and replaced with human genes disclosed herein, having different sequences at particular polymorphic positions. See, e.g., Coffman, Semin. Nephrol. 17:404, 1997; Esther et al., Lab. Invest. 74:953, 1996; Murakami et al., Blood Press. Suppl. 2:36, 1996. Such animals can be treated with candidate compounds and monitored for one or more clinical markers of cardiovascular status.

The following are intended as non-limiting examples of the invention.

### 20 Material and Methods

Genotyping of patient DNA with the Pyrosequencing<sup>TM</sup> Method as described in the patent application WO 9813523:

First a PCR is set up to amplify the flanking regions around a SNP. Therefor 2 ng of 25 genomic DNA (patient sample) are mixed with a primerset (20 - 40 pmol) producing a 75 to 320 bp PCR fragment with 0,3 to 1 U Qiagens Hot Star Taq Polymerase<sup>TM</sup> in a total volume of 20  $\mu$ L. One primer is biotinylated depending on the direction of the sequencing primer. To force the biotinylated primer to be incorporated it is used **3**0-0,8 fold.

For primer design, programms like Oligo 6<sup>TM</sup> (Molecular Biology Insights) or Primer Select<sup>TM</sup> (DNAStar) are used. PCR setup is performed by a BioRobot 3000 <sup>TM</sup> from Qiagen: PCR takes place in T1 or Tgradient Thermocyclers <sup>TM</sup> from Biometra.

The whole PCR reaction is transferred into a PSQ plate TM (Pyrosequencing) and prepared using the Sample Prep Tool TM and SNP Reagent Kit TM from Pyrosequencing according to their instructions.

## Preparation of template for Pyrosequencing TM:

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Sample preparation using PSQ 96 Sample Prep Tool:

- 1. Mount the PSQ 96 Sample Prep Tool Cover onto the PSQ 96 Sample Prep Tool as follows: Place the cover on the desk, retract the 4 attachment rods by separating the handle from the magnetic rod holder, fit the magnetic rods into the holes of the cover plate, push the handle downward until a click is heard. The PSQ 96 Sample Prep Tool is now ready for use.
- 2. To transfer beads from one plate to another, place the covered tool into the PSQ 96 Plate containing the samples and lower the magnetic rods by separating the handle from the magnetic rod holder. Move the tool up and down a few times then wait for 30-60 seconds. Transfer the beads into a new PSQ 96 plate containing the solution of choice.
- 25 3. Release the beads by lifting the magnetic rod holder, bringing it together with the handle. Move the tool up and down a few times to make sure that the beads are released.

All steps are performed at room temperature unless otherwise stated.

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# Immobilization of PCR product:

Biotinylated PCR products are immobilized on streptavidin-coated Dynabeads<sup>TM</sup> M-280 Streptavidin. Parallel immobilization of several samples are performed in the PSQ 96 Plate.

- Mix PCR product, 20 μl of a well optimized PCR, with 25 μl 2X BW-buffer II. Add 60-150 μg Dynabeads. It is also possible to add a mix of Dynabeads and 2X BW-buffer II to the PCR product yielding a final BW-buffer II concentration of approximately 1x.
- Incubate at 65°C for 15 min agitation constantly to keep the beads dispersed.
   For optimal immobilization of fragments longer than 300 bp use 30 min incubation time.

### Strand separation:

- 4. For strand separation, use the PSQ 96 Sample Prep Tool to transfer the beads with the immobilized sample to a PSQ 96 Plate containing 50  $\mu$ l 0.50 M NaOH per well. Release the beads.
- 5. After approximately 1 min, transfer the beads with the immobilized strand to a PSQ 96 Plate containing 99  $\mu$ l 1x Annealing buffer per well and mix thoroughly.
- 6. Transfer the beads to a PSQ 96 Plate containing 45 µl of a mix of 1x.

  Annealing buffer and 3-15 pmoles sequencing primer per well.
  - 7. Heat at 80°C for 2 minutes in the PSQ 96 Sample Prep Thermoplate and move to room temperature.
  - 8. After reaching room temperature, continue with the sequencing reaction.

### Sequencing reaction:

- 1. Choose the method to be used ("SNP Method") and enter relevant information in the PSQ 96 Instrument Control software.
- 5 2. Place the cartridge and PSQ 96 Plate in the PSQ 96 Instrument.
  - 3. Start the run.

### Genotyping using the ABI 7700/7900 instrument (TaqMan)

SNP genotypisation using the TaqMan (Applied Biosystems/Perkin Elmer) was performed according to the manufacturer's instructions. The TaqMan assay is discussed by Lee et al., Nucleic Acids Research 1993, 21: 3761-3766.

### Genotyping with a service contractor:

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Qiagen Genomics, formerly Rapigene, is a service contractor for genotyping SNPs in patient samples. Their method is based on a primer extension method where two complementary primers are designed for each genotype that are labeled with different tags. Depending on the genotype only one primer will be elongated together with a certain tag. This tag can be detected with mass spectrometry and is a measure for the respective genotype. The method is described in the following patent: "Detection and identification of nucleic acid molecules - using tags which may be detected by non-fluorescent spectrometry or potentiometry" (WO 9727325).

### Examples

To exemplify the present invention and it's utility (the imaginary) baySNP 28 will be used in the following:

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The nucleotide polymorphism found for baySNP 28 (e.g. C to T exchange) and the gene in which it presumably resides can be read from table 3. baySNP 28 was genotyped in various patient cohorts using primers as described in table 2. As a result the following number of patients carrying different genotypes were found (information combined from tables 3 and 5a):

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baySNP	Cohort	Total	-		
		TOTAL .	Genotype 11	Genotype 12	Genotype 22
			"CC"	"CT"	"77"
28	HELD_FEM_HIRESP	12	1 .	2	
28	HELD_FEM_LORESP	22			9
<u></u>	EORESP	.22	3	. 12	7

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When comparing the number of female patients exhibiting a high response to statin therapy (HELD\_FEM\_HIRESP) with the control cohort (HELD\_FEM\_LORESP) it appears that the number of low responders carrying the CT genotype is increased. This points to a lower statin response among female individuals with the CT genotype. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

BAYSNP	COMPARISON			
	COMPARISON	GTYPE	GTYPE	GTYPE
		CPVAL	XPVAL	LRPVAL
28	HELD_FEM_EFF	0,0506	0,0508	0,0442
			<del></del>	

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As at least one of the GTYPE p values is below 0,05 the association of genotype and statin response phenotype is regarded as statistically significant. I.e. the analysis of a patient's genotype can predict the response to statin therapy. In-more-detail-one-can-

calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain genotype (data taken from table 6a):

BAYSNP	COMPARISON	GTYPE1	GTYPE2	GTYPE3	RR1	RR2	RR3
28	HELD_FEM_EFF	CC	CT	TT	0,68	0,29	3,38

In case of baySNP 28 the risk to exhibit a high responder phenotype is 3,38 times higher when carrying the TT genotype. This indicates that a TT polymorphism in baySNP 28 is an independent risk factor for high statin response in females. On the other hand carriers of a CT or CC genotype have a reduced risk of being a high responder.

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In addition statistical associations can be calculated on the basis on alleles. This calculation would identify risk alleles instead of risk genotypes.

In case of baySNP 28 the following allele counts were obtained (data combined from tables 3 and 5a):

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baySNP	Cohort .	Total	Allele 1	Allele 2
•			" <b>C</b> "	"T"
28	HELD_FEM_HIRESP	12	4	20
28	HELD_FEM_LORESP	22.	18	26

When comparing the number of female patients with high statin response (HELD\_FEM\_HIRESP) with the control cohort (HELD\_FEM\_LORESP) it appears that the number of high responders carrying the T allele is increased, whereas the number of high responders carrying the C allele is diminished. This points to a higher statin response among female individuals with the T allele. Applying statistical tests on those findings the following p-values were obtained (data taken from table 5b):

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	BAYSNP		ALLELE CPVAL	ALLELE XPVAL	ALLELE LRPVAL
l	28	HELD_FEM_EFF	0,0411	. 0,0579	0,0349

As at least one of the ALLELE p values is below 0,05 the association of allele and statin response phenotype is regarded as statistically significant (in this example significant p values were obtained from two statistical tests). I.e. also the analysis of a patient's alleles from baySNP 28 can predict the extend of statin response. In more detail one can calculate the relative risk to exhibit a certain statin response phenotype when carrying a certain allele (data taken from table 6b):

baySNP	Allele 1	Allele 2						
	PAREIE I	Allele 2	COMPARISON	RR1	RR2			
28	С	T	HELD_FEM_EFF	0,42	The sale of the sa			
					2,39			

10 In case of baySNP 28 the risk to exhibit a high responder phenotype is 2,39 times higher when carrying the T allele. This indicates that the T allele of baySNP28 is an independent risk factor for a high statin response in females. In other words those patients should receive lower doses of statins in order to avoid ADR. However due to their 'high responder' phenotype they will still benefit from the drug. In turn carriers of the C allele should receive higher drug doses in order to experience a benefical 15 therapeutic effect.

Another example is (the imaginary) baySNP 29, which is taken to exemplify polymorphisms relevant for adverse drug reactions. baySNP 29 was found significant when comparing male patients with severe ADR to the respective controls (as defined in table 1b).

The relative risk ratios for the genotypes AA, AG and GG were as follows (data taken from table 6a):

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BAYSNP	COMPARISON	GTYPE1	GTYPE2	GTYPE3 RR		RR2	RR3
29	HELD_MAL_ADR5ULN	AA	· AG	· GG ·	3,15	0,66	0,32

In this case male patients carrying the AA genotype have a 3,15 times higher risk to suffer from ADR. In other words those patients should either receive lower doses of statins or switch to an alternative therapy in order to avoid ADR. On the other hand male patients with AG or GG genotypes appear to be more resistant to ADR and hence better tolerate statin therapy.

As can be seen from the following tables some of the associations that are disclosed in the present invention are indicative for more than one phenotype. Some baySNPs can for example be linked to ADR, but also to the risk to suffer from CVD (table 6).

### Sequences

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The sequence section contains all phenotype associated ('PA') SNPs and adjacent genomic sequences. The position of the polymorphisms that were used for the association studies ('baySNP') is indicated. Sometimes additional variations are found in the surrounding genomic sequence, that are marked by it's respective IUPAC code. Although those surrounding SNPs were not explicitly analyzed, they likely exihibit a similar association to a phenotype as the baySNP (due to linkage disequillibrium, Reich D.E. et al. Nature 411, 199-204, 2001).

Table 1a Definition of "good" and "bad" serum lipid levels

	"Good"	"Bad"
LDL-Cholesterol [mg/dL]	125 -150	170 - 200
Cholesterol [mg/dL]	190 - 240	265 - 315
HDL-Cholesterol [mg/dL]	60 -105	30 - 55
Triglycerides [mg/dL]	45 - 115 ·	170-450

<u>Table 1b</u> Definition of drug response phenotypes

Low responder	Decrease of serum LDL of at least 10% and at most 50% upon administration of 0.8 mg Control 10% and at most 50% upon
High responder	Decrease of serum LDL of at least 50% upon administration
Very low responder	Decrease of serum LDL of at least 10% and at most 25%
Very high	Decrease of serum LDL of at least 55% upon administration
responder Ultra low	0.4 mg Cerivastatin (female patients)  Decrease of serum LDL of at least 10% and at most 25% upon administration of 0.8 mg Cerivastating (female patients)
responder Ultra high	- Land Add Of O.O IIIV Left Vactoria / famala and and
responder	0.4 mg Cerivastatin (female patients)
Tolerant patient	myalgia or myopathy  AND
	serum CK levels below 70 mg/dl in women and below 80 mg/dl in men.
ADR patient (CK increase at least 2×ULN)	Diagnosis of muscle cramps, muscle pain, muscle weakness, myalgia or myopathy  OR
	serum CK levels higher than 140 mg/dl in women and 160 mg/dl in men.
Advanced ADR patient [ADR3] advanced CK ncrease, at least 8×ULN)*	Serum CK levels higher than 210 mg/dl in women and 240 mg/dl in men
Severe ADR patient [ADR5] severe CK ncrease, at least	Serum CK levels higher than 350 mg/dl in women and 400 mg/dl in men
×ULN)*	
when assembling	ng the cohorts for advanced and source ADD

<sup>\*:</sup> When assembling the cohorts for advanced and severe ADR we focused on the CK serum levels as those provide a more independent measure of statin related ADR.

<u>Table 1c</u> Definition of "high" and "low" serum HDL cholesterol levels

	Male	Female
	individuals	individuals
,High' HDL-Cholesterol [mg/dL]	>=80	>=104
,Low' HDL-Cholesterol [mg/dL]	<=35	<=37

An informed consent was signed by the patients and control people. Blood was taken by a physician according to medical standard procedures.

Samples were collected anonymous and labeled with a patient number.

DNA was extracted using kits from Qiagen.

# <u>Table 2</u> Oligonucleotide primers used for genotyping

Depending on the method used for genotyping different oligonucleotides were utilized. The table lists the various methods and primer sets that were used for this invention. Primers were designed using suitable programs like Primer Express<sup>TM</sup> (Applied Biosystems, Darmstadt, Germany) or Oligo<sup>TM</sup> (Molecular Biology Insights, Inc., Cascade, CO, USA).

Method	No. of oligonucleotides	Type of oligonucletides
Mass Spectrometry	4	2 Primers for preamplification of the genomic fragment, 2 allele specific primers with additional tag sequences for subsequent allele spec. PCR
Pyrosequencing™	3	2 Primers for preamplification of the genomic fragment (one biotinylated), 1 sequencing primer
ТаqМап	4	2 Primers for amplification of the genomic fragment, 2 allele specific probes carrying different fluorochromes (VIC, FAM) and a quencher.  Preferably the allele specific probes have a minor groove binder (MGB) attached (Kutyavin et al., Nucleic Acids Research 2000, 28:655-661).

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# PA SNPs, SNP classes and putative PA genes

Table 3

The baySNP number refers to an internal numbering of the PA SNPs. Listed are the different polymorphisms found in our association study. Also fion the association study we defined SNP classes; with ADR being adverse drug reaction related, with EFF being drug efficacy related and CVD being cardiovascular disease related. ADR3 and ADR5 relate to advanced and severe ADR, whereas VEFF and UEFF relate to very high/low and ultra high/low drug efficacy (see table 1b). Also accession numbers and descriptions of those gene loci are given that are most those skilled in the art in the Genbank database. The term 'SECONDARY' marks SNPs that do not reside inside the respective gene, but in homologous to the PA genes as listed in the sequences section (see below). Homologous genes and their accession numbers could be found by it's proximity. Null: not defined.

DESCRIPTION	Hunan T-lymphoma invasion and methers is industry.	Human T-Ivmphoma invasion and materials 1.1.	H. Sapiens pene for mitochondrial A The meters	Fluman beta adaptin mRNA complete A.	H.sapiens dek mRNA	Human flavin-containing monocourage (E)(O)	Human flavin-containing monooxyoenase (EMO1) mxxxx	Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethyl-	Homo sapiens 3-hydroxymethyl-3-methylelutaryl-Coenzyme & Lune (hudden)	glutaricaciduria) (HMGCL), mRNA	Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethyl-	glutaricaciduria) (HMGCL), nnRNA	
	HS162961	HS162961	X69907	M34175	X64229	M64082	M64082	NM_000191	1 _	161000 mix	NM_000191		
los uwas	8	99	99	Ħ	ŢĻ	AA	₹	₩	4 4	<u> </u>	¥¥		
diaday	AG	AG	8	T.	ঠ	AG	AG.	AG	AG A		AG		
KNR consider the Parallean version	A.A	AA	႘	ဥ	ည	SS	99	99	99		99		
	CVD	ADR3	CAD	CVD	CVD	ADRS	ADR3	ADRS	ADR3		ADR	-	
BANKSINIE	52	29	25	22	118	137	137	179	179		179	1	

<b>5</b>	38.	_	<del></del>	-	<del></del>																•			
DESCRIPTION FOR THE SHE SHOW TO SERVE SHOW THE S	Human beat-shock protein HSP70B' gene	Human heat-shock protein HSP70B' gene	Human heat-shock protein HSP70B' gene	H.sapiens SCA1 mRNA for ataxin	Human tumor necrosis factor type I receptor associated protein (TRAPI) mRNA, partial cds	H.sapiens mRNA for DLG2	Human slavin-containing monooxygenase (FMO1) mRNA, complete cds.	Homo sapiens mRNA for smooth muscle myosin heavy chain, partial eds.	Human lamin B2 (LAMB2) gene and ppv! gene sequence.	Human methylenetetrahydrofolate debydrogenase- methenyltetrahydrofolate	cyclohydrolase-formylterrahydrofolate synthetase mRNA, complete cds.	Homo sapicas methionine adenosyltransferase alpha subunit gene fragment.	CALCIUM-TRANSPORTING ATPASE PLASMA MEMBRANE, ISOFORMS 3A/3B (EC	Section Functs).	Human vascular endothelial growth factor gene, exon 1.	Homo sapiens WNT1 inducible signaling pathway protein 1 (WISP1) gene, promoter and	partial cds.	Homo sapiens (clones lambda gMHC 1,2,3 and 4) beta-myosin heavy chain (MYH7) gene.	complete cds.	Homo sapiens lipoprotein lipase precursor, gene, partial cds.	Human lissue factor gene, complete cds.	Homo sapieus mRNA for diacylglycerol kinase della, complete cds.	Human protein C inhibitor gene, complete cds.	
	H	XS1757	X51757	X79204	U12595	X82895	M64082	D10667	M94363	· J04031		143509	Q16720		M63971	AF223404		M57965		AF050163	102846	D73409	M64880	
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(PEZZ) A NOBICA GINESCERPPION CONTRACTOR OF THE	Human columdaditi	Human calmodulin mBNA	Human calmodulin mRNA complete cas.	Human Na.KATPase sulpinit alaka 2 (Armatas)	Human Na. K-A TPasse cohnicte chee, 2 (ATE 12.) gene, complete cds.	Human Na K-ATPage cultural alpha 2 (AIFIA2) gene, complete cds.	Human apolinoprotein A.F. and C. III. server.	Human apolitoparotein A. J. and C. III. come.	Human apolinoprotein A-I and C-III comes commits.	Hunan cardiac myosin heavy chain mDNA 2:	Homo sapiens B94 protein mRNA commissionals	H. Sanjens mRNA for activity bate Call.	H. Sapiens APXT mRNA	H saniens AP.2 here wane	H. sanieme mBNA for Allaria	Homo canione GDM DNA 6	Homo saniene GPV7 mDNA 6.	Homo saniens GPV1 mPNA for all the control of the c	Homo saniens GPVI mPNA for all the contract of	Homo saniens GPVI mpNA 6	Homo sapiens GPV/ mPNA for allered Bycoprotein VI-3, complete cds.	Homo sapieus GPVI mRNA for alliele el.	Human protein C inhibitor gene complete ade	יים האייוליוניוג הרושי
A NCBIC	J04046	J04046	J04046	105096	J05096	105096	100098	100098	36000f	M17712	M92357	X82540	X83543	Y09912			Ţ	1.	AB043821				M64880 H	
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BISNRGIA	CAD	VEFF	ADR	CVD	ADR3	ADRS	ADR3	CVD	ADR	CVD	CVD	ĊΛD	CVD	CVD	CVD	UEFF	EFF	ADR	VEFF	ADR3	UEFF .	ADR	ADRS	
BAXSIN	1757	1757	1757	1765	1767	1767	1837	1837	1837	1854	. 1862	2085	2093	2109	2124	2140	2140	2140	2140	2141	2141	2141	2186	<del></del> -
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VPE22 SELVICER DESCRIPTION	M64880 Human protein C inhibitor gene, complete cds.	M21616 Human platelet-derived growth factor (PDGF) receptor mRNA, complete eds.	M21616 Human platelet-derived growth factor (PDGF) receptor niRNA, complete cds.	M21616 Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	L36033 Human pre-B cell stimulating factor bomologue (SDF1b) mRNA, complete cds.	M15395 Human leukocyte adbesion protein (LFA-1Mac-1/p150,95 family) beta subunit mRNA.	X87872 H.sapiens mRNA for hepatocyte nuclear factor 4c	AB021744 Homo sapiens XIIIA gene for coagulation factor XIII A subunit, promoter sequence.	M11309 Human coagulation factor LX mRNA, complete cds.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	M63971 Human vascular endothelial growth factor gene, exon 1.	AJ246000 Homo sapiens mRNA for leucocyte adhesion receptor, L-selectin	Q92679 BETA-MYOSIN HEAVY CHAIN,	M15856 Human lipoprotein lipase mRNA, complete cds.	M18082 Human plasminogen activator inhibitor 2 (PAI-2) mRNA, complete cds.	AF084225 Homo sapiens cytochrome P450 2E1 (CYP2E1) mRNA, partial cds.	D63807 Human mRNA for lanosterol synthase, complete cds.	D63807 Humau mRNA for lanosterol synthase, complete cds.	104501 Human muscle glycogen synthase mRNA, complete cds.	J04501 Human muscle glycogen synthase mRNA, complete cds.	U49248 ABCC2: ATP-binding cassette, sub-family C (CFTR/MRP), member 2
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3152	VEFF	Į.	AT	AA.	131573	Human sulfite oxidate mBNA commissions
3214	VEFF	ຮ	8	99	1.39211	Homo sapiens mitochardrol
3215	ADRS	S	93	Ilua	L40027	Home saniene planages and the parmittee parmittee of the
3237	CVD	8	8	99	L41162	Home saniene college 11.
3241	ADR	Ħ	ב	8	L41668	Homo sapiens UDP-galactose-4-coimersee (GAIR) mNNA, complete cds.
3826	ADRS	8	AC	ΑĄ	BC006394	Homo sapiens, COX10 (yeast) homolog, cytochrome c oxidase assembly protein (heme A: farnesyltransferase)
3826	ADR3	೪	AC	₹	BC006394	Homo sapiens, COX10 (yeast) homolog, cytochrome c oxidase assembly protein (heme A:
3842	CAD	8	90	. noll	U12595	Human tumor necrosis factor true 1
3843	CVD	AA	AT	TI	U12595	Human tumor negrosis factor time 1 recently
3869	UEFF	පි	GŢ	TI	U17195	Homo sapiens A-kinase anchor protein (AK AP100) mRNA constitution
3942	UEFF	23	AC	₹	BC012063	Homo sapieus, Similar to retinoid X receptor, gamma, clone MGC:19909 IMAGE:4635470, mRNA, complete cds
4018	CVD	Ŧ	ದ	8	BC000011	Homo sapiens, mevalonate (diphospho) decarboxylase, clone MGC:1701 IMAGE:3505156,
4206	ADR3	AA AA	AT	E	BC000006	Home conjusted ATD.
4206	ADR	*	AT	E	Т	Home engine, A Track of the Company of the Sporting, beta I polypeptide
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4527	CAD	99	AG	*	$\top$	Heariers mbMA f.
4527	ADR3	99.	AG	AA	T	H saniens mRNA for manufactures.
4527	ADRS	99	AG	₩		H. sapieus mRNA for vacuolar H. 4 ATPana E. 1.1.
4544	ADR3	99	AG	AA.	NM_000755 H	ono sapiens carnifine acetyltrancfung (Ob and
					7	- continue accivitansierase (CKAI), nuclear gene encoding mitochondrial

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						protein, transcript variant 1, mRNA
4	ADR	. 00	PΑG	A.A	NM_000755	Homo sapiens camitine acetyltransferase (CRAT), nuclear gene encoding mitochondrial
						profein, transcript variant i, mr.v.A.
4545	ADR3	55	AG	. 44	552000 MN	Homo sapiens camitine acetyltransferase (CRAT), nuclear gene encoding mitochondrial
		}	?	į		protein, transcript variant 1, mRNA
5959	ADR	ی	٩٥	A A	NAM DOOTSE	Homo sapieus camitine acetyltransferase (CRAT), nuclear gene encoding mitochondrial
2	·	3	2		700	protein, transcript variant 1, mRNA
4668	ADRS	පි	AC	AA	HSKINAANP	H.sapiens mRNA for kinase A anchor protein
4669	EFF	ප	CJ	H	HSKINAANP	H.sapieus mRNA for kinase A anchor protein
4718	CAD	<del>D</del> D	AG	¥	Y09862	H. sapiens mRNA for legumain
4818	CAD	99	ΑĞ	A.A	AJ276181.	Homo sapiens partial ZNF202 gene for zinc finger protein homolog, exon 5
4827	ADRS	A.A.	AG	99	L07033	Human hydroxymethylglutaryl-CoA lyase mRNA, complete cds.
4838	CAD	ΑA	AG	99	L08246	Human myeloid cell differentiation protein (MCL.1) mRNA.
4856	ano	DG.	AG	llua ·	T11669	Human tetracycline transporter-like protein mRNA, complete cds.
4868	ADR	т	៦	႘	U83661	Homo sapiens multidrug resistance protein 5 (MRP5) mRNA, complete cds
4868	ADRS	TT	נז	8	U83661	Homo sapiens multidrug resistance protein 5 (MRP5) mRNA, complete cds
4887	. CVD	. 22	AC	AA	AC004264	Homo sapiens PAC clone RP1-102K2 from 22q12.1-qter, complete sequence.
4912	CVD	DD	AG	A.A.	M63971	Human vascular endothelial growth factor gene, exon 1.
4951	ADR3	ည	AG	₩	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
. 4951	ADRS	99	. AG	- AA -	AF091582.	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4951	ADR	99	· AG	₩	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4952	ADR3	Ħ	ರ	8	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
4952	ADRS	TI	5	ე	AF091582	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11
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		te cds.	le cds.		Human platelet-derived growth factor receptor alpha (PDGERA) mDNA	VANTA (VA	KA) mKNA	RA) mRNA	cds.		plete cds.		mplete cds.	mplete cds.	mplete cds.	mplete cds.	uplete cds.					ıë 22q12.3-1	art of the C	2 receptor be
		NA, comple	NA, comple	lete cds.	loba (PDC)	The Canada	pua (rugr	ptia (PDGF	I, complete		mRNA, con		(B) gene, co	В) gепе, со	В) депе, со	B) gene, co	B) gene, cor	•				chromoson	)), the 5° p	sting factor
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		Home grafies cytochrome P450 (CYP4F8) mRNA, complete cds.	tourn sepieus cytochrome P450 (CYP4F8) mRNA, complete cds.	Homo sapiens mRNA for calphobindin II, complete cds.	elet-derived	let-derived	let-derived	A for cami	Doorntein D		dulin mRN	tubule associ	- E330	monie-assoc	ubule-assoc	ubule-assoc	ubule-assoc	JEH Y DRO	ен урко	kin 6 mRN	RNA.	equence from	cytosouc n	cropnage lo
Niske Transition	Ношо варі	Homo cania	ordes ordes	Homo sapie	Human plate	Human platelet-derived growth factor recenter alsh (BDCE)	Human plate	Human mRNA for carnities and the contract of t	Human apolinopratein D. mp.N. A	Tuman colin	Human calmodulin mRNA complete cds.	Tuman micro	Himma	Author micromodic-associated protein 1B (MAP1B) gene, complete cds.	numan microtubule-associated protein 1B (MAP1B) gene, complete cds.	numan microhubule-associated protein 1B (MAP1B) gene, complete cds.	munian micrombule-associated protein 1B (MAP1B) gene, complete cds.	TINUVALE DEHYDROGENASE KINASE.	TANYALE DEHYDROGENASE KINASE.	numan interleukin 6 mRNA, complete cds.	Human bel-2 mRNA.	NORA man 6.2 6.12.3-13.2 Contains the	oranifords and cytosouc neurophil factor 4 (40kD), the 5' part of the CSF2RB gene for	Statutive yte-macrophage low-affinity colony stimulating factor 2 receptor beta, ESTs, STS
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NA.VA	BANNER (SINGLE) CHARMAN GEAREN GER	GUMIN	THE CHAPTE	Calabia	Z KANNOBE	Dincerpinon
		:				NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for
						granulocyte-macrophage low-affinity colony stimulating factor 2 receptor beta, ESTs, STS
					. •	Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13,2 Contains the
/1/6	ADRS	9	AG	AA	AL008637	NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part of the CSF2RB gene for
						granulocyte-macrophage low-affinity colony stimulating factor 2 receptor beta, EST3, STS
	1		-			Human DNA sequence from clone CTA-833B7 on chromosome 22q12.3-13.2 Contains the
5/17	Q S	99 : 90	AG	₩	AL008637	NCF4 gene for cytosolic neutroplul factor 4 (40kD), the 5' part of the CSF2RB gene for
						granulocyte-macrophage low-affinity colony stimulating factor 2 receptor beta, ESTs, STS
5850	CAD	GG	PAG.	¥¥	M95724	H. sapiens centromere autoantigen C (CENPC) mRNA, complete cds.
5959	CVD	99	AG	A.A	U12789	Human clone HSH1 HMG CoA synthase mRNA, partial cds.
6151	ADR	ຽ	AC	AA	U49245	Human geranylgeranyl transferase type II beta-subunit mRNA, complete cds.
6236	ADR	Ħ	ָל	ည	NM_000436	Homo sapiens 3-oxoacid CoA transferase (OXCT), nuclear gene encoding mitochondrial
						protein, mknA
6277	ADRS	F	. T2	9	NM_003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3.
		+				omong protein (FDX1), mRNA
6277	ADR	E	GT	.9	NM 003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
			·	•		binding protein (PDX1), mRNA
6277	ADR3	Ħ	5	S	NM 003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
						binding protein (PDX1), mRNA
6313	UEFF	8	ದ	Ш	X05199	Human mRNA for plasminogen
6369	CAD	т	Ct	ည	X52011	H.sapiens MYF6 gene encoding a muscle determination factor
6374	ADR3	TT.	2	ဗ	X52022	H.sapiens RNA for type VI collagen alpha3 chain
9689	CVD	TT	ಕ	႘	X54807	Human CYP2C8 gene for cytochrome P-450, 5' flank and exon 1
6486	CVD	99	AG	AA.	X69086	H sapiens mRNA for utrophin

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	DESCRIPTION	H. Saniens HNEA - DNA 6.	Hearing Dress and the factor of the factor o	transpierts mixiva for hepatocyte nuclear factor 4	n sapiens HNF4 mRNA for hepatocyte nuclear factor 4	H.sapiens HNF4 mRNA for hepatocyte nuclear factor 4	Happiens HNF4 mRNA for henatocyte muslage 6-11-1	Saniens HNEA mpNa 6.	Henricon many control legalocyte nuclear factor 4	Henrican Days 6	Example us to a supple of the	Home conjust B A C 1	Human mRNA for linearing.	Iman No K ATE	Himman Nig. V. A. Trus.	Amusan Na, AA. l'Asse subunit alpha 2 (ATP1A2) genc, complete cds.	riuman na, kA i Pase subunit alpha 2 (ATP1A2) gene, complete cds.	Human 111 4 P. Complete cds.	Human 117 A. B.	Home conjust B. C	stourd Saprens BAC clone CIB-60P12 from 7q21, complete sequence.	A DODGE LEADERS CAVEOLIN gene, promoter region and partial cds.	ABCB11: A1F-binding cassette, sub-family B (MDR/TAP), member 11	Homo saniens ATP cassette, sub-family B (MDR/TAP), member 11	Homo sapiens eviochrome PASO 2 A 1 (CARCI) mRNA, complete cds.	Sycamonic Faso 3A4 (CYPSA4) gene, promoter region.
	NCBI	X76930	0£692X	VZCOZY	Access	X76930	X76930	X76930				-					T								AF185589 Ho	
	27112	AA	A.A.	¥		¥¥	₩	g	TI	II	T	8	8	E	E	E	A.A.	99	gg	8	A.A.	₹	A.A.	gg	E	1
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BAYSNE	TO SECOND	0250	6520	6520	6522	. 6527	3	6524	9659	9659	9659	6734	6743	7128	7128	7128	7363	7409	7409	8138	8168	8210 A	8210		8249 A	

HENCERIES DIRSCRIPTION SERVICE	Homo sapiens cytochrome P450 3A4 (CYP3A4) gene, promoter region.	Human peroxisome proliferator activated receptor gamma 2 mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human platelet-derived growth factor (PDGF) receptor mRNA, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human microtubule-associated protein 1B (MAP1B) gene, complete cds.	Human pre-B cell stimulating factor homologue (SDF1b) mRNA, complete cds.	Human creatine kinase M mRNA, complete cds.	Homo sapiens lipoprotein lipase precursor, gene, partial cds.	Homo sapiens c-lbc mRNA for guanine nucleotide exchange factor Lbc, complete cds.	Homo sapiens c-lbc mRNA for guanine nucleonde exchange factor Lbc, complete cds.	Homo sapiens c-lbc mRNA for guanine nucleotide exchange factor Lbc, complete cds.	Homo sapiens A-kinase anchor protein (AKAP100) mRNA, complete cds.	Human CYP2C8 gene for cytochrome P-450, 5' flank and exon 1	Homo sapiens oxidase (cytochrome c) assembly 1-like (OXA1L), mRNA	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.	Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, complete cds.	Homo sapiens MSH55 gene, partial cds; and CLIC1, DDAH, G6b, G6c, G5b, G6d, G6e,	G6f, BAT5, G5b, CSK2B, BAT4, G4, Apo M, BAT3, BAT2, AIF-1, 1C7, LST-1, LTB,	TNF, and LTA genes, complete cds.
NGBI	AF185589	U63415	M21616	M21616	M21616	M21616	L06237	L06237	L06237	L36033	M14780	AF050163	AB055890	AB055890	AB055890	U17195	X54807	NM_005015	AF066859	AF066859		AF129756	
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BAYSNP SNP class   GTYPE11   GTYPE12	ב	· 93	ರ	ಚ	ಕ	AG	ಚ	ರ	៦	ე.	ಕ	AC	ည	8	ည	AG	CT	ָל	83	9 S		AG	
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SNPcles	ADRS	CAD.	ADR3	ADR	ADRS	ADR3	ADR	ENCLA	ADRS	CVD	ADR3	ADR3	VEFF	ADRS	· UEFF	ADRS	CVD	ADR3	UEFF	VEFF		CVD	
BAYSNR	8249	8480	8577	8577	. 8577	· 8578	8653	8653	8653	8816	8931	8943	9243	9243	9243	9523	9940	10001	10541	10541		00901 -	

Human acid alpha-glucosidase (GAA) mRNA, complete cds.  Human acid alpha-glucosidase (GAA) mRNA, complete cds.  Human acid alpha-glucosidase (GAA) mRNA, complete cds.  Human myoadenylate deaminase (GAA) mRNA, complete cds.  Homo sapiens protein phosphatase 2C alpha 2 mRNA, complete cds.	M34424 M34424 M34424 M34424 M60092 AF070670	8 8 8 8 5	ਰ ਹੋ ਹੋ ਹੋ ਹੋ ਦ	E E E E 8 8	ADR3 CVD ADR3 ADR3 CVD
Human acid alpha-glucosidase (GAA) mRNA, complete cds. Human acid alpha-plucosidasa (GAA), maxa	M34424 M34424	ප ප	t t	FF	DIG DIG
Human acid alpha-glucosidase (GAA) mRNA, complete cds.	M34424	පු	· CT	TT .	es l
Human, intestinal fatty acid binding protein gene, complete cds, and an Alu repetitive element.	M18079	8	៦	TT .	ADRS
Hurran, intestinal fatty acid binding protein gene, complete cds, and an Alu repetitive element.	M18079	႘	ರ	F	ADR3
Human, intestinal fatty acid binding protein gene, complete cds, and an Alu repetitive element.	M18079	හි	AG	AA	ADR3
Human, intestinal fatty acid binding protein gene, complete cds, and an Alu repetitive element.	M18079	8	AG	. <b>A</b> A	CAD
Human apolipoprotein E (epsilon-4 allele) gene, complete cds.	M10065	8	8	ß	田
Human apolipoprotein E (ensilon-4 allele) gene complete ad-	M10065	8	ខ	DD .	VEFF
Human apoliooprotein B-100 mRNA complete cds.	102610	AA	AG	99	CVD.
Hono satiens mRNA for asternishmen	D86425	99	AG	AA	CVD
Human mRNA for apolinoprofein E recentor 2 complete cas.	DS0678	පු	ರ	TI	CVD
Human mRNA for Xanitine delandronement	D11456	99	8	႘	CVD
Ruman mRNA for Xanthine debydrogenses complete cos.	D11456	8	ਬ	Ħ	CAD
Human mRNA for Xanthine delaydropenses Annual Control of the Contr	¥	AA	AG	9	CAD .
WINCE THE CONTROL OF THE PROPERTY OF THE PROPE	膼	12 GTYPE22	OLVE	BAYSVE SVP class   GTVRB11   GTVRB17   GT	SNRCE

	HAYSAT SNESTES (CTARDO) (CTARO) (GN	CTARD	GIME	COL KRESS	NGB/K	PENCEDIA DESCRIPTION CONTRACTOR OF THE PROPERTY OF THE PROPERT
11192	ADRS	ŧ	AT	4A	NM 003477	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
in the second					1	binding protein (PDX1), mRNA
11192	ADR3	Ţ	AT	AA	77 PEOD PEN	Homo sapiens Pyruvate dehydrogenase complex, lipoyl-containing component X; E3-
						binding protein (PDX1), mRNA
11248	ADR3	သ	ಶ	T.	X60435	H. sapiens gene PACAP for pituitary adenylate cyclase activating polypeptide.
11248	ADR	ဥ	ರ	TI	X60435	H.sapiens gene PACAP for pituitary adenylate cyclase activating polypeptide
11410	VEFF	99	GT	TI	AC004590	ABCC3: ATP-binding cassette, sub-family C (CFTR/MRP), member 3
11448	CVD	99	AG	AA	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11448	ADR	ÐÐ	AG	4A	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11450	CND	TI	AT	¥	AF050163	Homo sapiens lipoprotein lipase precursor, gene, partial cds.
11456	CVD	*	AG	99	AF051427	Homo sapiens estrogen receptor beta mRNA, complete cds.
11462	CVD	99	CT	11	AF051427	Homo sapiens estrogen receptor beta mRNA, complete cds.
11483	ADRS	Ŧ	ಭ	8	L19592	Homo sapiens interleukin 8 receptor alpha (IL8RA) gene, complete eds.
11483	ADR3	E	CT	ઇ	L19592	Homo sapiens interleukin 8 receptor alpha (IL8RA) gene, complete cds.
11483	ADR	TT.	ជ	8	L19592	Homo sapicas interleukin 8 receptor alpha (IL8RA) gene, complete cds.
11531	CAD	99	AG	AA	X52773	Human mRNA for retinoic acid receptor-like protein
			•			Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the
11536	CAD	<del>၂</del>	ં 8	. 99	AI 022721	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal
	_			:		Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome
			•			Proliferato
	•					Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the
11537	ADR	<b>{</b>	AG	ક	AL022721	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal
•					-, ·	Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisonne

					<u>_</u> :																	
PEAR AN KIGBLE OF DESCRIPTION TO THE PROPERTY OF THE PERSON OF THE PERSO	Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds.	Homo sapieus cytosolic phospholipase A2-gamma mRNA, complete cds.	Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, S'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5. flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens thrombin-activable fibrinolysis inhibitor gene, 5'-flanking region.	Homo sapiens chromosome 14q24.3 clone BAC270M14 transforming growth factor-beta 3 (TGF-beta 3) gene, complete cds; and unknown genes.	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	ABCB11: ATP-binding cassette, sub-family B (MDR/TAP), member 11	Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal	Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome	Proliferator delta	Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3. Contains the
NGBL	AB043943	AB043943	AF030555	AF058921	AF058921	AF080222	AF080222	AF080222.	AF080222	AF0802:22	AF107885	AF091582	AF091582	AF091582	AF091582	AF091582	AF091582		16766014			AL022721
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SNECHS	ADR3	ADRS	ADR3	ADR3	ADRS	ADRS	ADR3	ADR	ADRS	UEFF	ADR	ADR3	ADRS	ADR	UEFF	ADR	VEFF	•	ADRS			ADR
BAYEN	11727	11728	11914	11938	11938	11950	11950	11950	11951	11951	12008	12031	12031	12031	12032	12032	12032		12148			12148

G D11456   G D11456   G D11456   G D11456   E D11456   E D11456   E D1456   E D156982   E D156	Human clone HSH1 HMG CoA synthase inRNA, partial cds.	U12789	8	ts		=	ADR TI
G D11456 F G D1456 F G D15568 F G D15789 F G D1578	Human clone HSH1 HMG CoA synthase mRNA, partial cds.		ප		ರ	TT CT	E E
G D11456 F G D1456 F G D155168 F G D15	Human clone HSH1 HMG CoA syntlase mRNA, partial cds.		8		ಚ		Ŧ
A ALO22721   B	Human clone HSH1 HMG CoA synthase mRNA, partial cds.		ΑA		ΑG		g
A ALO22721   B	Human glycogen debrauching enzyme mRNA, complete cds.		ප		AC		· AA
A ALO22721   B   B   B   B   B   B   B   B   B	Human glycogen debranching enzyme mRNA, complete cds.	M85168	ည		AC	.AA AC	.AA
A ALO2721   B   B   B   B   B   B   B   B   B	Human cAMP-dependent protein kinase type I-alpha subunit (PRKARIA) mRNA, complete cds,	M33336	ප		ಕ	-	#
A ALO22721   B   B   B   B   B   B   B   B   B	Human cAMP-dependent protein kinase type I-alpha subunit (PRKARIA) mRNA, complete cds.	M33336	ខ		ដ	-	
A ALO2721   1   1   1   1   1   1   1   1   1	Human voltage-dependent anion channel isoform 1 (VDAC) mRNA, complete cds.	HSVDACIX	TT		AT		· AA
A AL022721 G D11456 G D11456 G D11456 G D86982	Human voltage-dependent anion channel isoform 1 (VDAC) mRNA, complete cds.	HSVDACIX			AT		ΑΑ
A ALO22721 G D11456 G D11456 G D186982 G D86982 EG D8698	Human mRNA for KIAA0229 gene, partial cds.	D86982	99	1.	AG	AA AG	AA
A ALO22721 G D11456 G D11456 G D86982 F	Human mRNA for KIAA0229 gene, partial cds.	D86982	99		AG	. AA AG	. AA
A ALO22721  G D11456  G D11456  G D11456  G D11456  F	Human mRNA for KIAA0229 gene, partial cds.	D86982	99	1	AG	AA AG	AA
A ALO22721  G D11456  G D11456  F G D11456  G D11456  F G D11456	Human mRNA for Xanthine dehydrogenase, complete cds.	D11456	99		AG	A'A AG	
A ALO22721 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Human mRNA for Xanthine dehydrogenese, complete cds.	D11456	99	l	AG	AA AG	AA
A AL022721	Homan mRNA for Xanthine dehydrogenase, complete cds.	D11456	99	ł	AG	AA AG	. AA
A AL022721	Proliferator delta				•		
A AL022721	Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxisome						
	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Ribosomal	AL022721	₩		AG	GG AG	
	Human DNA sequence from clone 109F14 on chromosome 6p21,2-21.3. Contains the						
	Proliferator della						
	Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxison						
	alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S Riboson						
	W DESCRIPTION TO THE PROPERTY OF THE PROPERTY		TYPE	9	GTVP 112 G		AGESTAN ONE CHEST IN LYBEIT (CITYPRIT) GIR

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13193	ADR3	99	AG	YW .	U12789	Human clone HSH1 HMG CoA synthase mRNA, partial cds.
13193	ADRS	99	AG	ΑA	U12789	Human clone HSH1 HMG CoA synthase mRNA, partial cds.
13338	UEFF	99	AG	₩.	U46023	Human Xq28 mRNA, complete cds.
13338	VEFF	ဌဌ	AG	A.A	U46023	Human Xq28 mRNA, complete cds.
13339	ADR	ဌ	AG	ΑΑ	U46023	Human Xq28 mRNA, complete cds.
. 13339	CVD	99	AG	AA	U46023	Human Xq28 mRNA, complete cds.
13340	VEFF	ဆ	. AC	¥¥	U46023	Human Xq28 mRNA, complete cds.
13479	UEFF	99	AG	₩	U95626	Homo sapiens ccr2b (ccr2), ccr2a (ccr2), ccr5 (ccr5) and ccr6 (ccr6) genes, complete cds,
						and lactoferrin (lactoferrin) gene, partial cds, complete sequence.
13633	ADR3	TT	ω	ຮ	HSGKTS1	H.sapieus mRNA for glycerol kinase testis specific 1.
13633	ADR	π	כגו	ខ	HSGKTS1	H.sapiens mRNA for glycerol kinase testis specific 1.
13929	ADR5	ÐÐ	94	AA	. L28101	Homo sapiens kallistatin (PI4) gene, exons 1-4, complete cds.
14065	EFF	သ	CT	Ħ	AC006022	Homo sapiens PAC clone RP5-1131G17 from 7p15.1-p14, complete sequence.
14083	ADR	TT	כז	8	AF044953	Homo sapiens NADH:ubiquinone oxidoreductase PGIV subunit mRNA, nuclear gene
						encoding mitochondrial protein, complete cds.
14085	EPF	Ħ	, t	) C	AFD44954	Homo sapiens NADH:ubiquinone oxidoreductase PDSW subunit mRNA, nuclear gene
						encoding mitochondrial protein, complete cds.
14087	FFF	· <b>E</b>	: : : :	<u>်</u> သ	AF044954	Homo sapieus NADH:ubiquinone oxidoreductase-PDSW subunit mRNA, nuclear gene
						encoding mitochondrial protein, complete cds.
14102	ADRS	<u>ප</u>	5	E	AF087661	Horno sapiens NADH-ubiquinone oxidoreductase 42 kDa subunit mRNA, complete cds,
						nuclear gene encoding mitachondrial protein.
14102	EFF	ຽ	ָט	Ħ	AF087661	Homo sapiens NADH-ubiquinone oxidoreductase 42 kDa subunit mRNA, complete cds,
				•		nuclear gene encoding mitochondrial protein.

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	HYDIN KINGGAN KINGGA GENERA	STATE OF	-	e a la se		NGBING PESCHIPHON AND THE CONTRACTOR OF THE CONT
						Human DNA sequence from clone CITF22-45Cl on chromosome 22 Contains the 3' part of
38559	es S	ខ	AC	¥	AL133392	the CSF2RB gene for low-affinity granulocyte-macrophage colony stimulating factor 2
•	·					receptor beta, the CSF2RB2 gene for colony stimulating factor 2 receptor beta 2, ESTs, STS
					·.	Human DNA sequence from clone CITF22-45Cl on chromosome 22 Contains the 3' part of
38959	EFF	8	AC	*	AL133392	the CSF2RB gene for low-affinity granulocyte-macrophage colony stimulating factor 2
		•		-		receptor beta, the CSF2RB2 gene for colony stimulating factor 2 receptor beta 2, ESTs, STS
39292	ADRS	ອອ	AG	AA	M33388	Human cytochrome P450 IID6 (CYP2D6) gene, complete cds.
39698	· ADR3	TI	ជ	ខ	61920X	Fuman mRNA for cytochrome P450 db1 variant b
39756	ADR3	11	ដ	ည	X58468	Human CYP2D7BP pseudogene for cytochrome P450 2D6
39951	ADR	E	t)	೪	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (ap1b3) gene, exon 7 and complete cds.
39951	ADRS	F	ಶ	႘	AF005896	Homo sapiens Na K-ATPase beta-3 subunit (atp1b3) gene, exon 7 and complete cds.
40466	नुस्	99	5	Ţ	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
40466	UEFF	99	15	E	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
40466	VEFF	ЭЭ	GT	TL	AB043821	Homo sapiens GPVI mRNA for platelet glycoprotein VI-3, complete cds.
44442	ADRS	ĄĶ	AG	99	NM_001931	Homo sapiens dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) (DLAT), mRNA
70555	a'V A	E	٤	ξ.	SECONDARY:	SECONDARY TO Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase
		•	;	3	NM_000191	(hydroxymethylglutaricaciduria) (HMGCL), mRNA
67555	ana	و	Ç	83	SECONDARY:	SECONDARY TO Homo sapiens 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase
21000		3	2	٤	NM_000191	(hydroxymethylglutaricaciduria) (HMGCL), mRNA
55670	VEITE	ر	£	<u>.</u>	SECONDARY:	SECONDARY TO Homo sapiens carnitine palmitoyltransferase I, liver (CPT1A), nuclear
		}	;		NM_001876	gene encoding mitochondrial protein, mRNA
55736	ADRS	₹	AĞ -	99	SECONDARY: M23234	SECONDARY TO ABCB4
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BANSHE SVRGBS GENYPELL GETYPETZ GENYPEZZ HIF NGBL EV DESGRIPTION WAS ARRESTED TO THE STATE OF TH	SECONDARY TO ABCB4	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA nuRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO Human 52-kD ribonucleoprotein Ro/SSA mRNA, complete cds.	SECONDARY TO H.sapiens centromere autoantigen C (CENPC) mRNA, complete cds.	SECONDARY TO H.sapiens centromere autoantigen C (CENPC) mRNA, complete cds.	SECONDARY TO H.sapiens centromere autoantigen C (CENPC) mRNA, complete cds.	SECONDARY TO H. sapiens centromere autoantigen C (CENPC) nıRNA, complete cds.	SECONDARY TO Homo sapiens COX10 homolog, cytochrome c oxidase assembly protein, heme A: farnesyltransferase (yeast) (COX10), nuclear gene encoding mitochoudrial protein, mRNA	SECONDARY TO Homo sapiens COX10 homolog, cytochrome c oxidase assembly protein, heme A: famesyltransferase (yeast) (COX10), nuclear gene encoding mitochondrial protein, nnRNA	
NCBL	SECONDARY: M23234	SECONDARY: M34551	SECONDARY; M34551	SECONDARY: M34551	SECONDARY: M3455	SECONDARY: M95724.	SECONDARY: M95724	SECONDARY: M95724	SECONDARY: S M95724	SECONDARY: S	SECONDARY: S. NM_001303 Pr	
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SNRcles	ADRS	ADR3	VEFF	ADR3	UEFF	ADR	ADR3	ADR	ADR3	ADR3	ADRS	
BAYSIN	55748	55813	55845	55845	55845	55923	55923	55945	55945	26007	26007	

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11095	ADRS	ÄÄ	AG	nu11	SECONDARY: NM_001303	SECONDARY TO Homo sapiens COX10 homolog, cytochrome c oxidase assembly protein, heme A: famesyltransferase (yeast) (COX10), nuclear gene encoding mitochondrial protein, mRNA
56104	UEFF	99	AG	AA	SECONDARY: AF091582	SECONDARY TO ABCB11
56113	ADRS	ĞĞ	GT	TT .	SECONDARY: AF091582	SECONDARY TO ABCB11
56113	ADR3	8	Œ	ΤŢ	SECONDARY: AF091582	SECONDARY TO ABCB11
56636	ADR	Tr	. CI	8.	SECONDARY: L13972	SECONDARY TO Homo sapiens beta-galactoside alpha-2,3-sialyltransferase (SIAT4A) mRNA, complete cds.
. 56636	ADR3	E.	บ	23	SECONDARY: . L13972	SECONDARY TO Homo sapiens beta-galactoside alpha-2,3-sialyltransferase (SIAT4A)
56636	ADRS	TT	נז	8	SECONDARY: L13972	SECONDARY TO Homo sapiens beta-galactoside alpha-2,3-sialyltransferase (SIAT4A) mRNA, complete cds.
26666	ADR3	99	AG	₩	SECONDARY: AF027406	SECONDARY: SECONDARY TO Homo sapiens muscle-specific serine kinase 1 (MSSK1) mRNA, AF027406 complete cds.
99995	ADRS	99	. AG	AA	SECONDARY: AF027406	SECONDARY TO Homo sapiens muscle-specific serine kinase 1 (MSSK1) mRNA, complete cds.
99995	ADR	DD	. PW.	. AA	SECONDARY: AF027406	SECONDARY TO Homo sapiens muscle-specific serine kinase 1 (MSSK1) mRNA, complete cds.
29995	EFF	TT	CT	သ	AF027406	Homo sapiens muscle-specific serine kinase 1 (MSSK1) mRNA, complete cds.
26667	ADR3	TT	CT	သ	AF027405	Homo sapiens muscle-specific serine kinase 1 (MSSKI) mRNA, complete cds.
26780	ADR3	gg	AG	AA .	SECONDARY:	SECONDARY TO Homo sapiens, ATPase, Na+/K+ transporting, beta I polypeptide

OR SHEWGING HONSON BUILDING TO SHEW SHEW SHEW SHEW SHEW SHEW SHEW SHEW	BC000006	SECONDARY: SECONDARY TO Homo sapiens, ATPase, Na+/K+ transporting, beta 1 polypeptide BC000006	SECONDARY: SECONDARY TO Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, AFIRESTO complete of		SECONDARY: SECONDARY TO Homo sapiens muscle glycogen phosphorylase (PYGM) mRNA, AF066859 complete cds.	SECONDARY: SECONDARY TO Human mRNA for Xanthine debydrogenase, complete cds.	SECONDARY: SECONDARY TO Human mRNA for Xanthine dehydrogenase, complete cds.	SECONDARY: SECONDARY TO Human mRNA for Xanthine dehydrogenase, complete cds.	SECONDARY: SECONDARY TO Human mRNA for Xanthine dehydrogenase, complete cds.	SECONDARY: SECONDARY TO Homo sapiens TSC2, NTHLI/NTH1 and SLC9A3R2/E3KARP genes, AB014460 partial and complete cds.	SECONDARY TO Human DNA sequence from clone 109F14 on chromosome 6p21.2-21.3.  SECONDARY: Contains the alternatively spliced gene for Transcriptional Enhancer Factor TEF-5, the 60S  AL022721 Ribosomal Protein RPL10A gene, a PUTATIVE ZNF127 LIKE gene, and the PPARD for Peroxicome Protiferator delta.	SECONDARY: SECONDARY TO Homo sapiens GPVI gene for platelet olurormiein VI and is fad.
1		SECONDARY BC00006	SECONDARY	SECONDARY AF066859	SECONDARY AF066859	SECONDARY: D11456	SECONDARY: D11456	SECONDARY: D11456	SECONDARY: D11456	SECONDARY: AB014460	SECONDARY: AL022721	SECONDARY:
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HAYS		26780	56876	56876	56876	56978	57000	57000	27000	57313	57734	57837

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IN DESCRIPTION OF THE PROPERTY	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO Homo sapiens GPVI gene for platelet glycoprotein VI, partial cds.	SECONDARY TO H.sapiens mRNA for 3-hydroxy-3-methylglutaryl coenzyme A synthase	SECONDARY TO Human Xq28 mRNA, complete cds.	SECONDARY TO Human Xq28 nıRNA, complete cds.	SECONDARY TO Human Xq28 mRNA, complete cds.		SECONDARY TO Homo sapiens putative N6-DNA-methyltransferase (N6AMT1), mRNA
AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: AB043943	SECONDARY: X83618	SECONDARY: U46023	SECONDARY: U46023	SECONDARY: U46023	SECONDARY: U46023	SECONDARY:
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Kalpasgaration and the property of the propert	. 688	SECONDARY TO nuclear hormone receptor PRR2 889	SECONDARY TO Human DNA sequence from clone CTA-833B7 on chromosome	RY: 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part	37 of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2	receptor beta	SECONDARY TO Human DNA sequence from clone CTA-833B7 on chromosome	SECONDARY: 22q12.3-13.2 Contains the NCF4 gene for cytosolic neutrophil factor 4 (40kD), the 5' part	of the CSF2RB gene for granulocyte-macrophage low-affinity colony stimulating factor 2	receptor beta	RY: SECONDARY TO Home sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	RY: SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	RY: SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	RY: SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	RY: SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	RY: SECONDARY TO Homo sapiens ADP/ATP carrier protein (ANT-2) gene, complete cds.	
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AF030555	SECONDARY TO Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds.	ECONDARY: SECONDARY TO Homo sapiens lanosterol synthase (2,3-oxidosqualene-lanosterol NM_002340   cyclase) (LSS), mRNA	Iomo sapiens lanosterol	SECONDARY TO Homo sapiens lanosterol synthase cyclase) (LSS), mRNA	domo sapiens lanosterol	SECONDARY TO Homo sapiens lanosterol synthase cyclase) (LSS), mRNA	SECONDARY: SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds. M34960	SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds.	SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds.	SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds.	SECONDARY TO Homo sapieus transcription factor IID mRNA, complete cds.	SECONDARY: SECONDARY TO Homo sapiens transcription factor IID mRNA. complete cds	
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DESCRIPTION - ALCOHOLOGICAL - ACCOUNTS - ACC	SECONDARY TO Homo sapiens transcription factor IID mRNA, complete cds.	SECONDARY TO Human glycogen debranching enzyme isoform I (AGL) mRNA,	alternatively spliced isoform, complete cds.	Homo sapiens putative N6-DNA-methyltransferase (N6AMTI), mRNA	Homo sapiens putative N6-DNA-methyltransferase (N6AMT1), mRNA	nuclear hormone receptor PRR2	nuclear hormone receptor PRR2	nuclear homone receptor PRR2	nuclear hormone receptor PRR2	Homo sapiens lipoprotein lipase precursor, gene, partial cds.	MTM1: myotubular myopathy 1	MTM1: myotubular myopathy 1.	MTM1: myotubular myopathy 1	MTM1; myotubular myopathy 1	MTMR2: myotubularin related protein 2	MTMR2: myotubularin related protein 2	MTMR2: myotubularin related protein 2	SLC24A3: solute carrier family 24 (sodium/potassium/calcium exchanger), member 3	Selenoprotein P genomic region	Selenoprotein P genomic region	Selenoprotein P genomic region
M34960	SECONDARY: M34960	SECONDARY:	U84007	NM_013240	NM_013240	NM_003889	NM_003889	NM_003889	NM_003889	AF050163	U46024	U46024	U46024	U46024	US8033	U58033	U58033	AF169257	AC008945	AC008945	AC008945
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DESCRIPTIONS		SECONDABY TO Home conjent mBNA for CAAA interaction acotain 4 (CDA)	SECONDANT TO INDIRESTINATE TO CHAPT-INICIALING PROCESS (CLT.4)	SECONDABY TO Home conjune mDNA for CArd3 internation protein 4 (CIBA)	SECONDAIN TO MOME Suprems many for Curaz-micracing protein 1 (Cura)	CECOND A DV TO Home majors and MA for Clark? interaction neglect (CDA)	(+ HO) + include sapidities for Aran, and Aran
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## Table 4 Cohorts

Given are names (as used in table 5) and formations of the various cohorts that were used for genotyping

COHORT	1 7 5
	Definition
HELD_ALL_GOOD/BAD	Healthy elderly individuals of both genders with good or bad serum lipid profiles (as defined in table 1a)
HELD_FEM_GOOD/BAD	Healthy elderly individuals (female) with good or bad serum lipid profiles (as defined in table la)
HELD_MAL_GOOD/BAD	Healthy elderly individuals (male) with good or had
CVD_ALL_CASE/CTRL	serum lipid profiles (as defined in table la) Individuals with diagnosis of cardiovascular disease
CVD_FEM_CASE/CTRL	and healthy controls (both genders)  Individuals with diagnosis of cardiovascular disease and healthy controls (female)
CVD_MAL_CASE/CTRL	Individuals with diagnosis of cardiovascular disease and healthy controls (male)
HELD_FEM_ADRCTRL	Female individuals that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_FEM_ADRCASE	Female individuals that exhibited ADR (as defined in table 1b) upon administration of periodeteria
HELD_MAL_ADRCTRL	Male individuals that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_MAL_ADRCASE	Male individuals that exhibited ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADRCTRL	Individuals of both genders that tolerate adminstration of cerivastatin without exhibiting signs of ADR (as defined in table 1b)
HELD_ALL_ADRCASE	Individuals of both genders that exhibited ADD (co.
HELD_FEM_LORESP	defined in table 1b) upon administration of cerivastatin  Female individuals with a minor response to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIRESP	Female individuals with a high response to to cerivastatin administration (as defined in table 1b)
HELD_FEM_HIHDL/LOHDL	Treatmy elderly individuals (female) with high or low
HELD_MAL_HIHDL/LOHDL	Healthy elderly individuals (male) with high or low serum HDL cholesterol levels (as defined in table 1c)
HELD_ALL_HIHDL/LOHDL	Healthy elderly individuals of both genders with high or low serum HDL cholesterol levels (as defined in table 1c)  table 1c)
HELD_FEM_ADR3CASE	Female individuals that exhibited advanced ADR (as
	defined in table 18) upon administration of cerivastatin

COHORT	Definition
HELD_MAL_ADR3CASE	Male individuals that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_ALL_ADR3CASE	Individuals of both genders that exhibited advanced ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_VLORESP	Female individuals with a very low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_VHIRESP	Female individuals with a very high response to cerivestatin administration (as defined in table 1b)
HELD_FEM_ADR5CASE	Female individuals that exhibited severe ADR (as defined in table 16) upon administration of cerivastatin
HELD_MAL_ADR5CASE	Male individuals that exhibited severe ADR (as defined in table 1b) upon administration of certivastatin
HELD_ALL_ADR5CASE	Individuals of both genders that exhibited severe ADR (as defined in table 1b) upon administration of cerivastatin
HELD_FEM_ULORESP	Female individuals with a ultra low response to cerivastatin administration (as defined in table 1b)
HELD_FEM_UHTRESP	Female individuals with a ultra high response to to cerivastatin administration (as defined in table 1b)

Table Sa and Sb Cohort sizes and p-values of PA SNPs

The baySNP number refers to an internal numbering of the PA SNPs. Cpval denotes the classical Pearson chi-squared test, Xpval denotes the exact version of Pearson's chi-squared test, LRpval denotes the likelihood-ratio chi-squared test.. Cpvalue, Xpvalue, and LRpvalue are Interscience 1993), and (A. Agresti, Statistical Science 7, 131 (1992)). The GTYPE and Allele p values were obtained through the respective 22 B; gehotypes as defined in table 3) resulting in the respective chi square test with a 3×2 matrix. For Allele p values we compared the allele calculated as described in (SAS/STAT User's Guide of the SAS OnlineDoc, Version 8), (L. D. Fisher and G. van Belle, Biostatistics, Wiley chi square tests when comparing COHORTs A and B. For GTYPE p value the number of patients in cohort A carrying genotypes 11, 12 or 22 (FQ11 A, FQ 12 A, FQ 22 A; genotypes as defined in table 3) were compared with the respective patients in cohort B (FQ11 B, FQ 12 B, FQ count of alleles 1 and 2 (A1 and A2) in cohorts A and B, respectively (chi square test with a 2×2 matrix). SIZE A and B: Number of patients in cohorts A and B, respectively. See table 4 for definition of COHORTs A and B.

Table 5a Cohort sizes and frequency of alleles and genotypes

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COHORTA FERMINAL	HELD_ALL_ADRCASESULN	CVD_FEM_CASE	CVD_MA1_CASE	HELD_ALL_ADRCASE3ULN	HELD_ALL_ADRCASE	HELD_ALL_ADRCASESULN	HELD_ALL_ADRCASEJULN	HELD_MAL_ADRCASE	HELD_MAL_ADRCASEJULN	HELD_MAL_ADRCASESULN	HELD_ALL_ADRCASESULN	HELD_FEM_BAD2	негр_ тем_сонос	HELD_ALL_CASEZ	CVD_ALL_CASE	HELD_FEM_CASE2	HELD_MAL_LOHDL	HELD_FEM_ADRCASE3ULN	HELD_MAL_ADRCASEJULN	HELD_FEM_VHIRESP	HELD_MAL_ADRCASESULN
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Э. СОНОВТЛЯ?	HELD_FEM_OLORESP	HELD_MAL_ADRCTRL	HELD_MAL_CTRL	HELD_ALL_CTRL	HELD_ALL_ADRCTRL	HELD_FEM_ULORESP	HELD FEM VLORESP	CVD_MAL_CTRL	HELD_ALL_HINDL	HELD_MAL_HIHDL	HELD-MAt-GOOD	HELD_MAL_GOOD	HELD_FEM_GOOD	CVD MAL CTRL	HELD_FEM_GOOD2	CVD_ALL_CTRL	HELD_ALL_GOOD2	HELD_ALL_GOOD	HELD_MAL_GOOD2	CVD_FEM_CTRL	HELD_MAL_GOOD
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A COHONIA CHEST	HELD_FEM_UHIRESP .	HELD_MAL_ADRCASESULN	HELD_MAL_CASE	HELD_ALL_CASE	HELD_ALL_ADRCASE3ULN	HELD_FEM_UHIRESP	HELD FEM VHIRESP	CVD_MAL_CASE	HELD_ALL_LOHDL	HELD MAL LOHDL	HELD WAL BAD	. מאם אאר חופו	HELD FEM BAD	CVD_MAL_CASE	HELD_FEM_BAD2	CVD_ALL_CASE	HELD_ALL_BAD?	HELD_ALL_BAD	HELD_WAL_BAD2	CVD_FEM_CASE	HELD_MAL_BAD
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HELD_FEM_GOOD	HELD_FEM_VLORESP	HELD_FEM_LORESP	CVD_FEM_CTRL	HELD_ALL_ADRCTRL	HELD_ALL_ADRCTRL	HELD_ALL_ADRCTRL	HELD_MAL_GOOD2	CVD_FEM_CTRL	HBLD_MAL_ADRCTRL	HEED_ALL-GOOD2	HELD_MAL_ADRCTRL	HELD_MAL_GOOD2	HELD ALL GOOD2	CVD_FEM_CTRL	HELD MAL ADRCTRL	HELD_ALL_GOOD	HELD_MAL_ADRCTRL	HELD_FEM_GOOD	HELD_ALL_CTRL2	HELD_FEM_ADRCTRL
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HELD_FEM_BAD	HELD_FEM_VHIRESP	HELD FEM HIRESP	CVD_FEM_CASE	HELD_ALL_ADRCASEDULN	HELD_ALL_ADRCASESULN	HELD_ALL_ADRCASESULN	HELD_MAL_BAD2	CVD_FEM_CASE	HELD_MAL_ADRCASESULN	HELD_ALL_BAD2	HELD_MAL_ADRCASESULN	HELD_MAL_BAD2	HELD_ALL_BAD2	CVD_FEM_CASE	HELD_MAL_ADRCASEJULN	HELD_ALL: BAD	HELD_MAL_ADRCASEJULN	HELD_FEM_BAD	HELD_ALL_CASE2	HELD_FEM_ADRCASESULN
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	89 71 27 35 18 HELD_FEM_GOOD 78 69 87 16 37	G A HELD_FEM_BAD 80 89 71 27 35 . 18 HELD_FEM_GOOD 78 69 87 16 37 G C HELD_FEM_VHIRESP 140 163 117 45 73 22 HELD_FEM_VLORESP 143 191 95 66 59	G A HELD_FEM_BAD 80 89 71 27 35 .18 HELD_FEM_GOOD 78 69 87 16 37	G A         HELD_FEM_GADD         80         89         71         27         35         18         HELD_FEM_GOOD         78         69         87         16         37           G C         HELD_FEM_VHIRESP         140         163         117         45         73         22         HELD_FEM_VLORESP         143         191         95         66         59           G C         HELD_FEM_HIRESP         269         319         219         92         135         42         HELD_FEM_LORESP         282         369         195         123         123           A G         CVD_FEM_CASE         18         2         34         0         2         16         CVD_FEM_CTRL         18         9         27         0         9	G A         HELD_FEM_BAD   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   18         78         18	10830   G   A   HELD_FEM_URADA   RO   89   71   27   35   18   HELD_FEM_GOOD   78   69   87   16   71   72   73   73   74   74   74   74   74   74	10930 G A HELD_FEM_VHIRESP 80 89 71 27 35 18 HELD_FEM_GOOD 78 69 87 16 37 25 110949 G C HELD_FEM_VLORESP 143 191 85 66 89 18 18 10949 G C HELD_FEM_VHIRESP 140 163 117 45 73 22 HELD_FEM_LORESP 222 369 195 173 123 36 18 19052 A G C HELD_ALL_ADRCAREL 18 7 75 19 28 19 0 HELD_ALL_ADRCTRL 18 7 77 6 19 2 7 0 9 9 19 10062 T C HELD_ALL_ADRCARELUM 47 77 20 27 20 0 HELD_ALL_ADRCTRL 175 175 61 65 43 9 10 10060 T C HELD_ALL_ADRCAREUM 47 77 80 27 27 20 0 HELD_ALL_ADRCTRL 126 179 77 6 3 3 3 10 10000 T C HELD_ALL_ADRCAREUM 47 175 18 18 16 10 0 HELD_ALL_ADRCTRL 106 175 179 179 63 53 10 10000 T C HELD_ALL_ADRCAREUM 57 18 18 16 4 10 3 HELD_AALL_GOODD 48 196 20 1 174 147 27 11000 T C HELD_AALL_ADRCAREUM 59 97 175 187 187 187 187 187 187 187 187 187 187	10830   G   A   HELD_FEM_GAND   B0   R9   71   Z7   S5   18   HELD_FEM_COOD   T8   69   R7   16   37   25   10949   G   C   HELD_FEM_CHRIESP   L40   L51   L17   L45   Z3   L15   L15	10930   C   HELD_FEN_URDSD   E0   S9   71   Z7   S5   S8   HELD_FEN_GOOD   T8   69   S7   IS   IS   IS   IS   IS   IS   IS	10930   C  A   HELD_FERA_RADD   RO   SO   TI   ZT   SS   SO   HELD_FERA_CLONESP   TS   TS   TS   TS   THELD_FERA_CLONESP   TS   TS   TS   TS   TS   TS   TS	10930   C   A   HELD_FEM_WINESPY   140   153   117   45   73   22   HELD_FEM_VLORESPY   143   151   55   65   59   18   110949   C   C   HELD_FEM_VHENESPY   140   153   113   22   115   22   HELD_FEM_VLORESPY   143   151   153

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00)		ELD A	SLD_M		LD FE	LD FE	LD MA	1 C 18		LD_AL	LD_ALL	מששי ע		D_MAI	D FEM	7.52	L rem	ָם אַנוֹי	D MAL	
a		+	+	$\dashv$			뽀	=		#	H	195		된	HBL	. 5		표 -	層	
			- (	>   ·	$\dashv$	<b>&gt;</b> .	<u> </u>	£	?   6	<b>⊃</b>	<u> </u>	c	> <	>	0	-	9 (	ו·	0	
ROLE INO		+	-		7 =	7	<u> </u>	8		>	<u> </u>	=	•   •	,	20	~	,   5	2	0	
P G EUN		-	7 7	2   5		;  ·	<u>م</u>	3	7	3   5	ţ.	11	1		<b>3</b> .	78	100	9	<i>ج</i> ر	]
(O)	46	:   <del>S</del>	}  -	=	2	!   (	<b>5</b>	185	3	-	^	34	75		=	3	3,6	;	<b>∞</b>	7
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	23	55	+-	=	- F	٥		276	26	42		17	12	1	5	3	136	1	~ ~	1
	HELD_ALL_ADRCASESULN	HELD_MAL_ADRCASEJULN	HELD_FEM_ADRCASESULN	SESULN	SEBULN	SESULN		Si Si	ESULN	EBULN		ESCIN	BULN	SE		BULN	SE .	N Ji	20LR	
HORT	ADRC	ADRCA	ADRCA	ADRCA	ADRCA	ADRCA		EN HES	ADRCAS	DRCAS		<b>EKCAS</b>	DRCAS	ADRC		DRCASE.	ADRCA	DRCASS	2000	
3	D ALL	LD MAL	LD FEM	HELD_FEM_ADRCASESULN	HELD_FEM_ADRCASEJULN	HELD MAL ADRCASESULN		neto_ren_HRESP	HELD_ALL_ADRCASESULN	HELD_ALL_ADRCASEBULN	7000	ALLE FOR AURCASESULN	HELD_MAL_ADRCASESULN	HELD FEM ADRCASE		HELD_FEM_ADRCASESULN	HELD_ALL_ADRCASE	HELD MAL ADREASESTER		
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## Table 5b p-values of PA SNPs

A SNP is considered as associated to cardiovascular disease, adverse statin response or to efficacy of statin treatment, respectively, when one of the p values is equal or below 0.05.

BAYSNE	GOMPARISON I			GIVE	ALLELA	ALLELE	7.95 (3) Y Y
29	HELD_FEM_LIP				GPVAL	XPVAL	LRPVAI
29		0,0996			0,0441	0,0533	0,0438
	HELD_ALL_ADRIULN		} '	0,0493	0,1053	-0,1185	0,1048
29	HELD_ALL_LIP	0,0912	. 1	0,091	0,0503	0,0625	0,05
52 .	HELD_ALL_CC	0,0112	0,0128	0,0099	0,0015	0,0023	0,0014
52	HELD_MAL_HDL	0,0237	0,0238	0,0194	0,8213	0,8292	0,8214
52	HELD_FEM_CC	0,0818	0,0956	0,08	0,0293	0,0436	0,0282
52	HELD_MAL_CC	0,1499	0,2053	0,1393	0,0303	0,0547	0,0282
·52	HELD_MAL_LIP2	0,1121	0,1133	0,1112	0,0423	0,0429	
57	HELD_FEM_CC	0,0168	0,008	0,0108	0,0076	0,0106	0,0422
118	HELD_MAL_LIP2	0,1081	0,1089	0,1043	0,0466		0,0049
137	HELD_MAL_ADRSULN	0,0575	0,0872	0,0156	0,0892	0,0501	0,0462
137	HELD_ALL_ADR5ULN	0,0307	0,0274	0,0218		0,1027	0,0951
137	HELD_ALL_ADR3ULN	0,034	0,035		0,2446	0,2504	0,2486
179	HELD_MAL_ADR5ULN	0,0094		0,0255	0,0671	0,0747	0,0686
179	HELD_MAL_ADR3ULN		0,0241	0,0154	0,9216	1	0,921
179	HELD_ALL_ADRSULN	0,0452	0,0479	0,0408	0,5445	0,7636	0,5327
179	HELD_ALL_ADR	0,0415	0,0537	0,0756	0,7311	0,8135	0,7272
240		0,0691	0,0447	0,0464	0.2487	0,3013	0,2482
	HELD_ALL_ADR3ULN	0,1154	0,1318	0,0756	0,04	0,0539	0,0281
240	HELD_MAL_ADR3ULN	0,0641	0,0976	0,0399	0,0835	0,1215	0,0507
241	HELD_ALL_ADR3ULN	0,0987	0,0984	0,1033	0,0237	0,0301	0,0262
241	HELD_ALL_ADRSULN	0,1495	0,1519	0,1611	0,04	0,0527	0,0464
241	HELD_MAL_ADR3ULN	0,1757	0,2127	0,1775	0,0411	0,055	0,0459
288	. CVD_ALL	0,1013	0,1098	0,0863	0,0462	0,0557	
384	CVD_ALL	0,0214	0,022	0,0205	0,1828		0,0441
384	HELD_FEM_CC	0,0793	0,0887	0,0704		0,1946	0,1831
533	CVD_ALL		0,0932	0,0905	0,0214	0,0299	0,021
542	HELD_FEM_ADR	<del></del>	0,0292		0,0387	0,0482	0,0359
		0,0322	0,0292	0,0417	0,0922	0,1056	0,0907

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BAYSN	PACOVEARISON			ERGIYE	Sanday Hares		
					ALLEL	APPRICATION AND NOT	E ALLELE
. 576	HELD ALL LIP	0,034			To the last of the Co.	Life Edited Same and Same	ERPVAI
576	HELD_FEM_LIP	0,040				0,0641	0,012
608	· CVD_MAL	0,003				0,0583	0,017
614	HELD_MAL_HDL	0,0069	, , , , , , , ,		0,0027	0,0035	0,0035
614	HELD_ALL_CC	0,0045				0,0001	0
614	HELD_MAL_CC	0,0694			0,0052	0,008	0,0047
614	HELD_MAL_LIP	0,1792			0,0102	0,0154	0,0101
614	CVD_ALL			0,1858	0,0113	0,0153	0,0123
614	HELD_FEM_CC	0,1654			0,0202	0,0237	0,0188
738	CVD_ALL	0,031	0,0198		0,0446	0,0537	0,0387
1056		0,0999			0,0261	0,0303	0,0257
1056	HELD_ALL_HDL	0,1007	0,1082	0,0989	0,0323	0,0468	0,0304
1092	HELD_FEM_LIP	0,0488	0,0518	0,0403	0,0695	0,09	0,0691
1524	HELD_MAL_ADRSULN		0,0443	0,0114	0,6514	0,7766	0,6465
	HELD_MAL_CC2	0,0122	0,0142	0,0107	0,0079	0,0113	0,0062
1524	HELD_ALL_LIP	0,0507	0,0381	0,0237	0,0592	0,0717	0,0581
1524	HELD_ALL_CC	0,0681	0,0671	0,0561	0,025	0,0318	0,0248
1574	. CVD_MAL	0,0611	0,0678	0,0422	0,3189	0,4133	0,3254
1582	HELD_MAL_ADR3ULN	0,1522	0,1512	0,0956	0,0468	0,0648	0,0295
1657	HELD_FEM_EFF	0,05	0,0604	0,047	0,4599	0,5588	0,459
1722	CVD_MAL	0,013	0,0128	0,0135	0,3717	0,4376	0,3729
1756	HELD_MAL_ADR5ULN	0,0321	0,0857	0,1003	0,0402	0,063	
1757	HELD_ALL_CC	0,02	0,0205	0,0053	0,3618		0,068
1757	HELD_FEM_CC	0,0517	0,0569	0,015	0,1242	0,386	0,3603
1757	HELD_FEM_VEFF	0,1217	0,1247	0,1208	0,0423	0,1342	0,1193
1757	HELD_MAL_ADR	0,0536	0,05	0,0501		0,0505	0,0422
1765	HELD_ALL_LIP	0,0466	0,0494	0,0442	0,6703	0,7693	0,6702
1767	HELD_ALL_ADR3ULN	0,0032	0,0075		0,3068	0,3533	0,3058
1767	HELD_ALL_ADR5ULN	0,0608	0,0467	0,0036	0,0053	0,0066	0,0026
1767	HELD_MAL_ADRSULN	0,183		.0,0302	0,0196	0,0231	0,0086
1767	HELD_FEM_ADR3ULN		0,216	0,0679	0,075	0,1229	0,0194
1767	TYPEY A	0,0371	0,0348	0,0221	0,0341	0,0408	0,0251
1837			0,1875	_0,1061	0,0606	_0,0741	-0,0334
	TUTE VINKOUTU	0,0408	0,0398	0,0402	0,0225	0,0282	0,0196

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	ANT PROPERTY OF CHARACTER PROPERTY OF THE PERSON OF THE PE	CPV	AT XPY	L IRPV	LI CPYAI		LRPVA
1837	HELD_FEM_LIP	0,033	0,035	6 0,032	A. 1874 A. M.	Transfer to the	A 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
1837	HELD_ALL_LIP	0,046	6 0,04	6 0,045			-,-:
1837	HELD_ALL_ADR	0,05	2 0,048	8 0,0514			-,,,,,
1854	HELD_FEM_LIP	0,051	2 0,052	7 0,05	0,0661	0,07	0,0708
1862	HELD_FEM_LIP	0,056	2 0,058	0,0534		0,0264	0,0658
2085	HELD_FEM_CC	0,014	9 0,010	. 1			0,0229
2085	HELD_ALL_CC	0,038		· ·		0,0096	0,0081
2093	HELD_MAL_CC	0,047			0,0185	0,02	0,0183
2093	HELD_ALL_CC	0,1590				0,002	0,0013
2109	HELD_MAL_HDL	0,0044				0,0501	0,0383
2109	HELD_ALL_HDL	0,0187		, , , , , ,		0,0543	0,0299
2109	HELD_ALL_LIP2	0,0438			0,059	0,065	0,0546
2109	HELD_FEM_LIP	0,0612		-	0,015	0,0152	0,0148
2124	HELD_MAL_LIP	0,1532		-	0,0214	0,0277	0,0209
2140	HELD_FEM_UEFF	0,1332			. 0,0434	0,0557	0,0433
2140	HELD_FEM_EFF	0,0437			0,009	0,0116	0.0069
2140	HELD_MAL_ADR				0,0082	0,009	0,008
2140	HELD_FEM_VEFF	0,0596		0,0227	0,0301	0,0429	0.0285
2141	HELD_MAL_ADRIULN	0,0915	0,0872	0,0888	0,0284	0,0379	0,0277
2141	HELD_FEM_UEFF	0,0844	0,0968	0,0461	0,0218	0,0238	0,0116
2141		0,0776	0,0859	0,0221	0,1372	0,1469	0.1323
2186	HELD_MAL_ADR	0,0548	0,0515	0,0254	0,0347	0,0399	0,0344
2187	HELD HELD SULN	0,0287	0,0843	0,1009	0,0498	0,0718	0,0798
2192	HELD_FEM_ADR3ULN	0,0517	0,0567	0,0507	0,0495	0,0613	0,0529
	HELD_FEM_ADR	0,0008	0,0011	0,0003	0,0011	0,0014	0,0004
2192	HELD_FEM_ADR3ULN	0,0114	0,0187	0,0015	0,0146	0,0232	0,0019
	HELD_ALL_ADR	0,0234	0,0113	0,0173	0,0053	0,0068	0.0044
	HELD_FEM_ADR5ULN	0,0613	0,1149	0,0155	0,073	0,1305	0,0181
	HELD_ALL_ADR3ULN	0,1807	0,1865	0,1212	0,0607	0,0756	
2203	HELD_FEM_LIP	0,0132	0,011	0,0126	0,0101	0,0118	0,039
2203	HELD_ALL_LIP	0,0296	0,0294	0,029	0,042		0,0098
2217	HELD_MAL_CC	0,0089	0,0048	0,0053	0,0074	0,0442	0,0422
2217	CVD_FEM	0,1624	0,1741	0,1076	0,0384	0,0101	0,0071
				-,	v,v364	0,0539	0,0314

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BAXSN	Person				ALL	EV ALEED	
2281	HELD_FEM_CC	0,042	2 0,043		î ceyaî	a free classical and a second	LRPVA
2281	HELD_MAL_CC	0,052					0,0072
2284	HELD_MAL_LIP	0,075				0,1238	0,0807
2290	HELD_MAL_CC					0,0292	0,0137
2327	HELD_MAL_ADR	0,030			0,0022	0,0031	0,0017
2327	HELD_MAL_ADRSUL	0,0279		7	0,0923	0,1092	. 0,092
. 2327	HELD_MAL_ADR3ULN				0,3085	0,4458	0,3068
2327	<del></del>				0,0919	0,116	0,0897
2353	HELD_FEM_EFF	0,0462			0,0998	0,1039	0,0998
2353	CVD_MAL	0,0703		0,0139	0,0223	0,0233	0,0031
	HELD_ALL_CC	0,0255		0,0224	0,0659	0,0929	0,0654
2353	CVD_ALL	0,1352	0,1146	0,0973	0,0468	0,0506	0,0347
2353	HELD_FEM_CC	0,0743	0,0491	0,0628	0,1836	0,3092	0,1885
2371	HELD_ALL_LIP2	0,018	0,018	0,0181	0,043	0,0444	0,0432
2376	HELD_ALL_LIP2	0,03	0,038	0,0302	0,0327	0,0411.	0,0329
2401	HELD_FEM_UEFF	0,0263	0,0256	0,0266	0,1128	0,1233	0,1146
2463	HELD_ALL_CC	0,0122	0,0147	0,0028	0,0144	0,0168	0,0033
2463	HELD_FEM_CC	0,0257	0,0328	0,0074	0,0307	0,0376	0,0033
2463	HELD_FEM_LIP2	0,0915	0,0988	0,0431	0,7177	0,7419	0,718
2755	HELD_FEM_ADR	0,0203	0,0192	0,0178	0,0222	0,024	
2755	HELD_ALL_ADR	0,0325	0,035	0,03	0,0499	0,024	0,022
2755	HELD_FEM_EFF	0,0455	0,0449	0,0446	0,4065	0,4262	0,0496
2925	HELD_FEM_VEFF	0,0168	0,0169	0,0162	0,0055	0,4262	0,4065
2925	HELD_FEM_UEFF	0,0184	0,0176	0,0181	0,009		0,0055
3043	HELD_FEM_ADR3ULN	0,031	0,0498	0,0233	0,009	0,0119	8800,0
3152	HELD_FEM_VEFF	0,0204	0,0206	0,0196		0,0764	0,0376
3214	HELD_FEM_VEFF	0,0379	0,0331	0,0261	0,3254	0,333	0,3253
3215	HELD_MAL_ADR5ULN	0,0093	0,1304		0,4369	0,4475	0,437
3237	HELD_FEM_CC	0,0174	0,0276	0,041	0,0096	0,1304	0,0423
3241	HELD_MAL_ADR	0,111	0,1115	0,0167	0,0218	0,0323	0,0211
3826	HELD_MAL_ADRSULN	0,2155	0,1113	0,1048	0,0334	0,0418	0,033
	HELD_ALL_ADR5ULN		0,1993	0,0862	0,0716	0,1186	0,0187
	TELT NAME OF THE PARTY OF THE P			_0,1522	-0,0707	0,0873	-0;038
		U, Z.J.Z.Q	0,2755	0,1635	0,0732	0,1143	0,044

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	P GOVERNISON			e e ye		MALLEL	EALEE
3842				LTREVA	I CPYAI	XOVAI	
	CVD_ALL	0,009	6 0,0142	0,0014	0,0108	0,0157	0,0016
3842	CVD_MAL	0,068	2 0,0966	0,0207	0,0735	0,1027	0,0222
3842	CV.D_FEM	0,071	7 0,1136	0,0359	0,0751	0,1165	0,0376
3843	HELD_MAL_CC2	0,020	7 0,0236	0,0084	0,0758	0,1046	0,0759
3843	HELD_FEM_HDL	0,0447	7 0,024	0,0146	0,1239	0,1687	0,1233
3869	HELD_FEM_UEFF	0,0491	0,0538	0,0488	0,0211	0,0244	0,0202
3942	HELD_FEM_UEFF	0,0206	0,0152	0,0122	0,0028	0,0041	
4018	HELD_MAL_LIP	0,1128	0,1214		0,037	0,0451	0,0029
4206	HELD_ALL_ADR3ULN	0,1055	0,1128	0,1103	0,041	0,0532	0,0313
4206	HELD_FEM_ADR	0,1218		0,1193	0,0436		0,0418
4206	HELD_ALL_ADRSULN	0,1204		0,1254	0,0472	0,0574	0,0434
4527	· CVD_ALL	0,0044		0,0012	0,0472	0,0639	0,0488
4527	HELD_FEM_LIP2	0,0441	0,0429	0,0424	0,2436	0,2844	0,2451
4527	HELD_MAL_CC	0,0814	0,0496	0,0661	0,0147	0,0157	0,0145
45.27	HELD_MAL_CC2	0,0599	0,0604	0,0583	4	0,0296	0,0197
4527	HELD_ALL_ADR3ULN	0,0688	0,0608	0,0728	0,0256	0,0378	0,0267
4527	HELD_ALL_CC2	0,1329	0,1396		0,0316	0,0402	0,0354
4527	HELD_ALL_ADRSULN	0,0796	0,0668	0,1355	0,0449	0,048	0,0461
4544	HELD_MAL_ADR3ULN	,	<u> </u>	0,1142	0,0478	0,0592	0,0569
4544	HELD_MAL_ADR	0,0731	0,0154	0,0146	0,0043	0,0062	0,0063
4544	HELD_ALL_ADR	0,086	0,0643	0,0601	0,0283	0,0348	0,0274
4544	HELD_ALL_ADR3ULN		0,0869	0,0832	0,0279	0,0308	0,0276
4545	HELD_MAL_ADR3ULN	0,1284	0,1257	0,1312	0,0497	0,054	0,0537
4545	HELD_MAL_ADR	0,0116	0,0154	0,0146	0,0043	0,0062	0,0063
4545		0,0629	0,0569	0,0516	0,0234	0,0247	0,0226
4668	HELD_ALL_ADR	0,0947	0,0982	0,0917	0,0318	0,0385	0,0314
4669	HELD_ALL_ADRSULN	0,0773	0,0782	0,0348	0,1143	0,1279	0,1111
4718	HELD_FEM_EFF	0,1061	0,1031	0,1053	0,0415	0,0458	0.0412
4818	HELD_MAL_LIP	0,0234	0,0261	0,006	0;2267	0,2838	0,2221
	HELD_MAL_LIP	0,0117	0,0073	0,0072	0,0904	0,1138	0,0946
	HELD_MAL_ADR5ULN	0,0267	0,0922	0,0873	0,6447	0,708	0,6539
4838	HELD_ALL_CC2	0,1354	0,1425	0,1366	0,047	0,0495	0,0469
<del>1856</del>	CVD_MAL	0,0123	0,0338	0,0089	0,0129	0,0349	0,0094

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	E COMPARISON	という れんりんりゃける		E GTVP	E ALLEL L CPVAI	E SALUE	
4868	HELD_MAL_ADR	0,049	2 0,055			Character of the state of the	ERPYA
4868	HELD_MAL_ADRSUL		.,				0,2117
4887	HELD_MAL_CC	0,0119				0,5267	0,4261
4887	HELD_ALL_CC	0,0826				0,0077	0,0042
4912	HELD_MAL_LIP					0,0429	0,0378
4951	HELD_ALL_ADR3ULN	0,2542	_		0,0325	0,053	0,0303
4951	HELD_FEM_ADR3ULN				0,5543	0,6301	0,5547
4951					0,237	0,284	0,2372
4951	HELD_FEM_ADR5ULN		0,0039	0,0088	0,0663	0,0845	0,0657
4951	HELD_ALL_ADRSULN		0,0054	0,0103	0,0586	0,0675	0,0589
<u> </u>	· HELD_FEM_ADR	0,0104	0,0096	0,0091	0,1202	0,1247	0,12
4951	HELD_ALL_ADR	0,0233	0,0229	0,022	0,1271	0,1376	0,1269
4952	HELD_ALL_ADR3ULN	,	0,0017	0,0015	0,6771	0,7182	0,6774
4952	HELD_FEM_ADR3ULN	1	0,0017	0,002	0,2491	0,2848	0,2496
4952	HELD_FEM_ADRSULN	0,0029	0,0023	0,0048	0,0938	0,1245	<del></del>
4952	HELD_ALL_ADR5ULN	0,0062	0,0056	0,009	0,1013	0,1264	0,094
4966	HELD_MAL_LIP	0,0276	0,027	0,0099	0,0138	<del></del>	0,102
4966	HELD_MAL_ADR	0,0409	0,046	0,0375		0,0207	0,0122
4966	HELD_FEM_CC .	0,0951	0,1056	0,0936	0,0937	0,1211.	0,0933
5019	CVD_FEM	0,0011	0,001		0,0442	0,0696	. 0,0434
5019	HELD_ALL_CC2	0,0043	0,0045	0,0007	0,0055	0,0087	0,0053
5019	HELD MAL HDL	0,0666		0,0043	0,0479	0,0599	0,0477
5019	HELD_ALL_LIP		0,0705	0,0594	0,0076	0,0117	0,0068
5019	HELD_MAL_CC2	0,0362	0,0383	0,0342	0,0109	0,0125	0,0108
	HELD_FEM_ADR3ULN	0,0182	0,0179	0,0186	0,0143	0,0167	0,0138
L		0,0193	0,0172	0,0174	0,064	0,0907	0,0714
5165	HELD_MAL_ADRSULN	0,0267	0,0922	0,0873	0,6447	0,708	0,6539
	HELD_FEM_ADR	0,0405	0,0271	0,0268	0,2071	0,2511	0,2059
	HELD_FEM_ADR5ULN	0,0414	0,0557	0,0471	0,0836	0,1012	0,101
	HELD_MAL_ADRSULN	0,0556	0,0596	0,1196	0,046	0,0769	0,0577
5287	HELD_FEM_VEFF	0,0487	0,0497	0,0438	0,0093	0,0101	
5320	CVD_FEM	0,0342	0,0343	0,0283	0,0279		0,0088
5324	HELD_FEM_VEFF		0,0915	-0,0898		0,0303	0,0274
5373 I	TITE D. DO		0,0124	0,0056	0,0318	0,0391	0,0317
<del></del>			-,0127	0,000,0	0,0061	0,0088	0,0028

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5373	HELD_ALL_ADRSULN	J 0,0776		7 19 19 19 19	SALES VALOR IN	XPVAL	LRPVA
5375	HELD_FEM_ADRSULN				0,0287	0,0398	0,0217
5375	HELD_ALL_ADR5ULN			-	0,0058	0,0081	0,0027
5376	HELD_MAL_ADRSULN				0,0585	0,0615	0,0495
5377	HELD_FEM_ADR				0,0069	0,1212	0,0386
5377		0,0201		0,019	0,2353	0,2692	0,2345
5517	HELD_FEM_ADRSULN				0,0289	0,044	0,0203
5518	HELD_MAL_ADR	0,0831		0,0317	0,4341	0,6834	0,4294
5564	HELD_FEM_ADR5ULN			0,0637	0,0346	0,1839	0,0647
5569	CVD_MAL	0,0139	0,0146	0,0159	0,1077	0,1348	0,1057
	HELD_MAL_ADR5ULN		0,1304	0,0676	0,0445	0,0667	0,0238
5569	HELD_ALL_ADR5ULN	1 '	0,1504	0,0609	0,0502	0,0672	0,04
5716	HELD_ALL_ADR3ULN	,	0,0064	0,0069	0,0024	0,0025	0,0023
5716	HELD_FEM_ADR3ULN	0,0071	0,0063	0,0059	0,0027	. 0,0037	0,0024
5716	HELD_ALL_ADR5ULN	0,0248	0,0232	0,0218	0,0092	0,0124	0,0092
5716	HELD_FEM_ADRSULN	0,0769	0,0784	0,0685	0,0334	0,0412	0,0321
5717	HELD_ALL_ADRSULN	0,1212	0,1272	0,097	0,0433	0,049	0,0427
5717	CVD_FEM	0,0496	0,0575	0,0431	0,0551	0,0634	0,054
5850	HELD_MAL_CC	0,0304	0,0344	0,0113	0,1197	0,1794	0,1186
5959	CVD_MAL	0,064	0,0647	0,0552	0,0467	0,0678	0,048
6151	HELD_MAL_ADR	0,0502	0,0501	0,0488	0,3223	0,3964	0,3221
6236	HELD_ALL_ADR	0,0472	0,051	.0,0424	0,0867	0,0953	0,0864
6277	HELD_FEM_ADR5ULN	0,0014	0,0053	0,0049	0,0127	0,0215	
6277	HELD_ALL_ADRSULN	0,0041	0,0135	0,026	0,0832	0,1012	0,0185
6277	HELD_FEM_ADR	0,0251	0,0239	0,0079	0,0352		0,0964
6277	HELD_FEM_ADR3ULN	0,0147	0,0126	0,0119	0,0167	0,0186	0,0149
6313	HELD_FEM_UEFF	0,0369	0,0357	0,0376	0,1201	0,02	0,0196
6369	HELD_FEM_LIP	0,1311	0,145	0,1269		0,1519	0,1204
6374	HELD_ALL_ADR3ULN	0,0338	0,0325	0,0352	0,0461	0,0594	0,0457
6374	HELD_MAL_ADR3ULN	0,0498	0,0564		0,0091	0,0107	0,0099
6396	HELD MAL CC	0,0165	0,0238	0,044	0,011	0,0152	0,0121
6396	HELD_ALL_CC	0,0528	0,0238	0,0048	0,0233	0,031	0,0066
6396	CVD_FEM.	0,0328		0,0496	0,0334	0,0403	0,0323
		V,1144	0,0874	0,0928	0,046	0,0631	0,0442

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6396	CVD_ALL	0,138	8 0,121			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	LRPVA
6486	HELD_ALL_CC2	0,144					0,0465
6520	HELD_MAL_ADR5UL					0,0528	0,0345
6520	HELD_MAL_ADR3UL		_		7,000	0,3068	0,2137
6520	HELD_ALL_ADR5UL	-	-,-			0,2122	0,1939
6520	HELD_MAL_ADR					0,0892	0,093
6522	HELD_FEM_ADR3ULN	0,074			0,322	0,3417	0,3212
6522	HELD_FEM_ADR				0,2761	0,3091	0,284
6524		0,0523			0,0894	0,0983	0,0882
6596	HELD_MAL_ADR3ULN		0,0213	0,0096	0,0128	0,0173	0,0106
6596	HELD_FEM_ADR3ULN		0	O.	0	0,0001	0
	HELD_FEM_ADR5ULN	, ,	0,0006	0,0004	0,0001	1100,0	0,0008
6596	HELD_ALL_ADR3ULN	0,0003	0,0006	0,0005	0,0005	0,001	0,001
6596	HELD_FEM_ADR	0,0008	0,0011	0,0005	0,0014	0,0018	0,0009
6596	HELD_ALL_ADRSULN	0,0025	0,0064	0,0064	0,0036	0,0085	<del> </del>
6596	HELD_ALL_ADR	0,0199	0,0229	0,0186	0,0253	0,0286	0,0094
6734	HELD_ALL_CC	0,04	0,0752	0,0208	0,0463	0,0286	0,0236
6743	HELD_ALL_ADR	0,0299	0,0298	0,0293	0,5743		0,0241
7128	HELD_ALL_ADR3ULN	0,0099	0,0103	0,0081.	0,0032	0,6388	0,5742
7128	HELD_FEM_ADR3ULN	0,0161	0,014.	0,0134		0,0042	0,0021
7128	HELD_ALL_ADR5ULN	0,0787	0,0793		0,011	0,0121	0,0085
7128	HELD_FEM_ADR	0,0447	0,0497	0,0702	0,029	0,0316	0,0217
7128	HELD_FEM_ADR5ULN	0,0996		0,0437	0,0497	0,0519	0,0496
7363	HELD_FEM_LIP		0,1085	0,0925	0,0561	0,0763	0,0458
7363	HELD_ALL_LIP	0,0763	0,0816	0,0701	0,0282	0,0385	0,0276
	HELD_FEM_ADRSULN	0,0741	0,0762	0,0712	0,0298	0,0314	0,0299
		0,0051	0,0049	0,01	0,0025	0,0051	0,0054
	HELD_FEM_ADR3ULN	0,0303	0,0175	0,0316	0,0135	0,0165	0,0172
8138	HELD_MAL_ADR5ULN	0,1823	0,1987	0,0669	0,0691	0,128	0,017
	HELD_MAL_LIP	0,0177	0,0193	0,0183	0,0079	0,0088	0,0069
3138	HELD_MAL_CC	0,0107	0,011	0,0077	0,4323	0,4651	0,4318
3138		0,0401	0,039	0,0399	0,0761	0,0923	
168		0,0229	0,0222	0,026	0,011	0,0203	0,0757
168	HELD_FEM_LIP	0,0241	0,0204	0,0226	0,1027	0,0203	0,0132

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8210	HELD_ALL_ADR3UL	0,009		- and but all the state that the state of	ANG THE PARTY NAMED IN	2011 6.25 429 (\$42.50)	LRPVA
8210	HELD_FEM_ADR3UL					0,8049	0,7818
8210	HELD_FEM_ADR	0,022				0,4314	0,4063
8210	HELD_ALL_ADR	0,021		0,0198	0,2153	0,2257	0,2151
8241		0,0187			0,2277	0,2424	0,2276
8241	HELD_ALL_LIP	0,159			0,0063	0,0082	0,0058
8249	HELD_ALL_ADR3ULN	,	.   ' ' '		0,0425	0,0474	0,0407
8249	HELD_ALL_ADR5ULN				0,0458	0,0517	0,0569
8480	CVD FEM	0,0462			0,0527	0,0943	0,0765
8480	CVD_MAL	0,1317			0,0026	0,0039	0,0008
8577	HELD_ALL_ADR3ULN	1		0,0466	0,0145	0,0286	0,0026
8577	HELD_ALL_ADR	0,0786	0,0657	0,0615	0,0252	0,0333	0,0264
8577	HELD_ALL_ADRSULN	0,0786	-	0,0779	0,0341	0,0374	0,0339
8578	HELD_ALL_ADR3ULN		0,1417	0,1606	0,05	0,0577	0,0532
8653	HELD_MAL_ADR	0,0857	0,0895	0,0777	0,0407	0,0491	0,0421
8653	HELD_MAL_ADR3ULN	0,0015	0,002	0,0012	0,004	0,005	0,0032
8653	HELD_MAL_ADRSULN		0,0118	0,0049	0,0239	0,0259	0,0099
8653	HELD_ALL_ADR3ULN	0,0243	0,0358	0,0061	0,0499	0,0688	0,0107
3816	,	0,0509	0,0714	0,04	. 0,0799	0,1109	0,0679
3816	HELD_FEM_LIP2	0,0115	0,0116	0,0106	0,0057	0,0067	0,0056
8816	HELD_FEM_HDL	0,0254	0,0258	0,0184	0,0126	.0,0148	0,0119
8816	HELD_ALL_CC2	0,0198	0,0205	0,0188	0,0352	0,0373	0,0354
3816	CVD_ALL	0,0862	0,084	0,0801	0,0253	0,0334	. 0,0231
3816	HELD_FEM_CC2	0,0732	0,0788	0,0699	0,0263	0,0349	0,0263
8931	HELD_MAL_HDL	0,0827	0,0805	0,0459	0,9552	1	0,9552
3943	HELD_FEM_ADR3ULN	0,0638	0,0558	0,0365	0,1009	0,1129	0,0851
243	HELD_MAL_ADR3ULN	0,115	0,1264	0,0702	0,0366	0,0409	0,0217
243	HELD_FEM_VEFF	0,0407	0,0439	0,0252	0,155	0,1691	0,1544
<u> </u>	HELD_MAL_ADRSULN	0,1035	0,0777	0,0285	0,2159	0,2497	0,1855
243 ·	HELD_FEM_UEFF	0,1004	0,12	0,0335	0,1733	0,2118	0,1696
		0,0425	0,0646	0,0613	0,0575	0,0785	0,0889
940		0.0213	0,0425	0,0073	0,0294	0,0542	0,0099
940	HELD_ALL_CC	0,0341	0,0266	0,0312	0,0231	0,0354	0,0225

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1000		CPV	XPV	î î Rev	L CPVA	L XPVA	是有人的人,但是不是一个的。 第一个人的人们是一个人的人们是一个人们的人们的人们们们们们们们们们们们们们们们们们们们们们们们们们们们们们们们
10091		N 0,085			The state of deep at the	ALL REAL STREET, STREE	120 July 1997
10541	TIDES A EMI_UEFF	0,034	9 0,019	1 0,0267	0,0305		
10541	- CIM_VEFF	0,06	6 0,048	4 0,0643	0,0206		
10600	4.5	0,047	5 0,035	9 0,0348	0,0046		0,0029
10600		0,020	7 0,029	8 0,0058	0,0231-		0,0029
10600		0,056	0,113	7 0,0231	1	0,1228	
10745	HELD_MAL_LIP	0,092	6 0,0862	0,085	0,056	0,0701	0,0256
10748	HELD_MAL_LIP	0,140	0,1855	_ i	0,05	0,0676	0,0491
10749	HELD_FEM_LIP	0,0593	1_		0,0232	0,0376	0,0547
10785	· CVD_MAL	0,1111	0,1415		0,0383		0,023
10811	HELD_FEM_LIP2	0,0827			0,0442	0,0491	0,0448
10811	CVD_ALL	0,1149			0,0524	0,0465	0,0435
10830	HELD_ALL_LIP2	0,0065	1_	, , , , , , , , , , , , , , , , , , ,		0,0646	0,0498
10830	HELD_ALL_LIP	0,0187		1	0,0036	0,0039	0,0036
10830	HELD_MAL_LIP2	0,0389			0,0037	0,0048	0,0037
10830	CVD_FEM	0,0268			0,011	0,0112	0,0109
10830	HELD MAL LIP	0,0742	-	0,0238	0,0125	0,0141	0,0121
10830	HELD_FEM_LIP	0,1364	0,0873	0,0613	0,0224	0,0279	0,0219
10949	HELD_FEM_VEFF		0,1403	0,134	0,0428	0,0556	0,0426
10949	HELD_FEM_EFF	0,0543	0,0577	0,0536	0,0352	0,0374	0,0351
10962	CVD_FEM	0,0748	0,0744	0,0743	0,0356	0,04	0,0356
10962	HELD_ALL_ADR3ULN	0,0113	0,0275	0,0091	0,0218	0,0457	0,0177
10966		0,1473	0,1615	0,043	0,2642	0,3199	0,258
10966	HELD_ALL_ADR3ULN	0,1289	0,1277	0,0351	0,1511	0,1736	0,1447
11000	HELD_ALL_ADRSULN	0,1509	0,1612	0,0683	0,0587	0,0794	0,0483
11000	HELD_MAL_LIP2	0,0379	0,0378	0,0375	0,0125	0,0143	0,0123
11000	CVD_FEM	0,0202	0,0198	0,0161	0,9584	1	0,9584
	HELD_MAL_ADR3ULN	0,0414	0,0384	0,0554	0,0307	0,0378	0,0344
11000	HELD_ALL_LIP2	0,0965	0,0965	0,096	0,0351	0,0358	0,0348
11000	HELD_MAL_ADRSULN	0,0477	0,0555	0,0971	0,053	0,0607	
11001	HELD_MAL_LIP2	0,03	0,0288	0,0297	0,0103		0,0618
11001	HELD_ALL_LIP2	0,0662	0,0652	0,0658	0,0103	0,0111	0,0102
1001	CVD_FEM	0,0325	0,0293	0,0266		_0,0241	_0,0232
				0,0200	0,9749	1	0,9749

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11001	HELD_MAL_ADR3UL	Transaction Inches	A PARTITION OF STATE	ERPVA	2019年10年10日	XPVAL	ERPVAL
11001	HELD_ALL_LIP		_		0,0307	0,0378	0,0344
11020	HELD_MAL_ADR3ULI	0,111			0,0482	0,057	0,0473
11073	HELD_FEM_LIP				0,0596	0,0761	0,049
11073		0,111			0,0331	0,0361	0,0328
11192	HELD_ALL_CC2	0,096			0,0453	0,0475	0,0437
11192.	HELD_FEM_ADR5ULN			0,0329	0,2812	0,2901	0,2893
	HELD_FEM_ADR3ULN	1	0,0216	0,0353	0,2446	0,3079	0,249
11248	HELD_FEM_ADR3ULN	0,0183	0,0153	0,0137	0,025	0,0322	0,0203
11248	HELD_ALL_ADR	0,1078	0,1144	0,1071	0,042	0,0434	0,0419
11410	HELD_FEM_VEFF	0,0091	0,0089	0,0085	0,088	0,0909	0,0879
11448	HELD_MAL_HDL	0,0019	0,0012	0,0015	0,0002	0,0003	0,0002
11448	HELD_MAL_LIP	0,0055	0,0027	0,0061	0,0034	0,005	0,0042
11448	HELD_MAL_LIP2	0,0059	0,0056	0,0058	0,0233	0,0245	<u> </u>
11448	HELD_ALL_LIP2	0,0108	0,0106	0,0109	0,0119	0,0124	0,0234
11448	HELD_ALL_HDL	0,0647	0,0708	0,0648	0,0138	0,0215	0,012
11448	'HELD_FEM_ADR	0,0637	0,0601	0,0603	0,0162	0,0199	0,0142
11448	HELD_ALL_ADR	0,0576	0,0568	0,055	0,017		0,0156
11448	HELD_ALL_CC	0,0976	0,1314	0,0453	0,0671	0,0209	0,0166
11450	HELD_MAL_LIP	0,0068	0,0052	0,0066	<u> </u>	.0,0727	0,0652
11456	CVD_FEM	0,0026	0,0043	0,0016	0,0007	0,0012	0,0009
11462	HELD_MAL_LIP2	0,0302	0,0225	0,0284	0,0038	0,0058	0,0023
11462	HELD_ALL_LIP2	0,0406	0,0368		0,0091	0,0109	0,0091
11483	HELD_FEM_ADRSULN	0,032	0,0368	0,0362	0,0384	0,0431	0,0387
11433	HELD_FEM_ADRJULN	0,0442		0,0589	0,0562	0,0771	0,0832
11483	HELD_FEM_ADR	0,0628	0,034	0,0495	0,0824	0,0989	0,0958
11531	HELD_FEM_CC		0,0468	0,045	0,1531	0,2	0,1477
11536	HELD_ALL_CC	0,1229	0,1273	0,0498	0,0189	0,0335	0,0137
11537	HELD_MAL_ADR	0,0789	0,085	0,0365	0,7564	0,8525	0,7562
11558		0,1696	0,1625	0,1616	0,0467	0,0604	0,0455
1558	HELD_MAL_LIP2 HELD_ALL_LIP2	0,0028	0,0023	0,0028	0,0058	0,0064	0,0058
1558		0,011	0,0105	0,011	0,005	0,0054	0,005
1585	HELD_ALL_CC	0,0533	0,0503	0,05	0,102	0,1242	0,1013
	HELD_MAL_CC	0,0414	0,0372	0,0136	0,0108	0,0193	0,0094

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11594		S S		LRPVA	C CPVA	XPVAI	ERPVA
		0,081	9 0,099	0,035	0,0195	0,0196	0,0069
11594	HELD_MAL_ADR	0,031	2 0,040	3 0,0277	0,0365	0,0462	0,0324
11614	HELD_FEM_CC	0,047	0,0577	7 0,0234	0,0572	0,0644	0,0587
11614	HELD_MAL_CC2	0,052	0,0518	0,0331	0,0346	0,0482	0,0373
11614	HELD_ALL_CC	0,0923	0,1151	0,0429	0,25	0,2653	0,2502
11614	HELD_ALL_HDL	0,0563	0,0558	0,0499		1	0,9149
11631	HELD_MAL_ADRSULN	0,0386	0,0478	0,0304	0,0117	0,0156	
11631	HELD_MAL_ADR3ULN	0,1371	0,1283		0,046	0,0572	0,0155
11637	HELD_FEM_LIP	0,0168	0,0155		0,0321		0,051
11637	HELD_ALL_LIP	0,0303			0,0321	0,0343	0,0317
11637	CVD_MAL .	0,0697	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0,0767		0,0186	0,0149
11,637	CVD_ALL	0,0723			0,0248	0,0373	0,0272
11641	HELD_MAL_ADR	0,0142	0,0141	0,0129	0,0254	0,0318	0,0262
11645	HELD_FEM_CC	0,0369	0,0544		0,126	0,1468	0,1257
11646	HELD_FEM_LIP	0,0865	0,0938	0,0366	0,0456	0,0639	0,0454
11646	HELD ALL LIP	0,0788	0,0938	0,0854	0,0359	0,0387	0,0356
11652	HELD MAL LIP	0,0422	<del> </del>	0,078	0,0438	0,0453	0,0431
11727	HELD_ALL_ADRSULN		0,0402	0,0403	0,9398	. 1	0,9398
11727	HELD_MAL_ADR3ULN		0,0169	0,001	0,0033	0,0029	0,0001
11727	HELD_MAL_ADRSULN	0,0139	0,0156	0,0019	0,0035	0,0042	0,0002
11727	HELD_ALL_ADR3ULN	0,0632	0,0556	0,0165	0,0205	0,0202	0,003
11727		0,0384	0,0373	0,0163	0,0076	0,0071	0,0036
11728	HELD_FEM_ADRSULN	0,1918	0,2611	0,0649	0,0728	0,128	0,0182
	HELD_ALL_ADR5ULN	0,1462	0,1458	0,095	0,0556	0,0654	0,0388
11938	HELD_MAL_ADR3ULN	0,2466	0,3289	0,2216	0,0257	0,0387	0,0248
<del></del>	HELD_ALL_ADRIULN	0,0089	0,0095	0,0046	0,392	0,459	0,3897
	HELD_ALL_ADRSULN	0,0169	0,0157	0,0114	0,8154	0,8766	0,815
	HELD_FEM_ADR3ULN	0,0449	0,0479	0,0352	0,6253	0,6469	0,6247
		0,0201	0,0516	0,0044	0,0125	0,0113	
		0,0154	0,0166	0,0066	0,0323		0,0014
1950	HELD_MAL_ADR	0,0516	0,0613	0,0496	0,3586	0,0548	0,0214
	HELD_MAL_ADRSULN	0,0424	0,0545	0,0114		0,4444	0,3582
1951	7777		0,0235	0,0107	0,0236	0,0423	0,0037
				3,0107	0,0733	0,0868	0,0749

BAYSN	E COMPARISON			ECEVE	ELAELEL	E, ALCEL	EALLE
12000		CPV.	L xeva	LRPVA		XPVAI	
12008	HELD_ALL_ADR	0,048	5 0,062	0,0449		11, 12, 12, 12, 14, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15	0,048
12031	HELD_ALL_ADR3ULI	1 -	8 0,002	4 0,0026	. 0,63	0,7148	0,630
12031	HELD_FEM_ADRSUL	V 0,004	6 0,003	0,0086	0,0566		0,056
12031	HELD_ALL_ADRSULI	0,004	7 0,004	0,0086			0,050
12031	HELD_FEM_ADR3UL	0,005	5 0,0063	0,006	0,2925	0,3532	
12031	HELD_ALL_ADR	0,013	0,0141	1		0,113	0,292
12031	HELD_FEM_ADR	0,0147	0,0143		0,1206	0,1247	0,103
12032	HELD_FEM_UEFF	0,0304	0,0139	_ {	0,0076		0,120
12032	HELD_FEM_ADR	0,1261			0,0343	0,0093	0,0078
12032	HELD_ALL_ADR	0,0928				0,0448	0,031
12032	HELD_FEM_VEFF	0,0639		0,0517	0,0359	0,0376	0,0341
12148	HELD_MAL_ADR5ULN	, ,	1 3,0 .02		0,0748	0,0929	0,0737
12148	HELD_MAL_ADR	0,0376		0,026	0,0087	0,0155	0,0126
12148	HELD MAL ADRIULN		1, ,	0,0328	0,0142	0,0207	0,0139
12207	HELD_MAL_ADRSULN			0,085	0,0349	0,046	0,0398
12207	HELD_MAL_ADR	0,0034	0,0036	0,002	0,6147	0,7792	0,6195
12207	HELD_MAL_ADR3ULN		0,0028	0,002	0,1131	0,1259	0,1125
12399	HELD_MAL_ADRSULN	ļ	0,0181	0,0298	0,5888	0,6671	. 0,5919
12399	HELD_MAL_ADR3ULN		0,0336	0,0287	0,0338	0,0497	0,0552
12399	HELD_ALL_ADR		0,0602	0,0433	0,0568	0,0858	0,0714
12554	HELD_MAL_ADR	0,1174	0,109	0,1156	0,0393	0,0481	0,0386
12554		0,0489	0,0266	0,0384	0,0217	0,0303	0,0198
12851	HELD_FEM_VEFF	0,0785	0,0754	0,0774	0,0335	0,0365	0,0329
12851	HELD_FEM_ADR5ULN	0,0841	0,0704	0,087	0,0401	0,0635	0,0488
	HELD_MAL_ADR	0,0496	0,0509	0,0432	0,6573	0,6625	0,6573
	HELD_MAL_ADR3ULN	0,0572	0,0578	0,0424	0,8568	1	0,8564
13025	HELD_FEM_ADRSULN	0,0508	0,0491	0,0749	0,2494	0,3182	0,2546
13191	HELD_ALL_CC	0,0795	0,0789	0,0666	0,0287	0,0329	
	HELD_MAL_ADR3ULN	0,0028	0,0047	0,0052	0,2629	0,3274	0,0278
		0,0306	0,0985	0,1047	0,6516	0,7437	0,2753
		0,0459	0,0411	0,0633	0,9559		0,6584
13192		0,0927	0,0909	0,0428	0,7098	0.747	0,9559
3193	HELD_MAL_ADRIULN	0,0022	0,0038	0,0046		0,743	0,7097
				7,0070	0,2596	0,3258	0,2719

	P COMPARISON I			L GTYP	e cevai	E ALCEI	E ALLEI
13193	HELD_MAL_ADR5UL	N 0,02	27 0,088			The state of the s	
13193	HELD_ALL_ADR3UL	3					
13338	HELD_FEM_UEFF	0,031					0,9355
13338	HELD_FEM_VEFF	0,030				0,5935	
13339	HELD_MAL_ADR	0,035			0,8319	0,8624	-
13339	CVD_FEM	0,136			0,4768	0,5694	0,4767
13340	HELD_FEM_VEFF	0,015				0,0803	0,0465
13479	HELD_FEM_UEFF	0,106				0,0095	0,0072
13633	HELD_FEM_ADRIVLN	a de la companya de l	_L ' ' '			0,0364	0,0351
13633	HELD_FEM_ADR	0,113			0,0317	0,037	0,0361
13929	HELD_MAL_ADRSULN				0,0387	0,0448	0,0384
14065	HELD_FEM_EFF	0,087		- 7,200	0,1262	0,2119	0,0423
14083	HELD_FEM_ADR	0,069			0,0307	0,037	0,0303
14085	HELD_FEM_EFF	0,009			0,0353	0,0459	0,034
14087	HELD FEM EFF	0,0509	-		0,1267	0,1326	0,126
14102	HELD MAL ADRIULN	i i			0,1138	0,1184	0,1138
14102	HELD_FEM_EFF				.0,8445	1	0,844
14103	HELD_FEM-EFF	0,1217		0,1207	0,0351	0,0391	0,035
14103	HELD_FEM_VEFF	0,003	0,0023	0,0004	0,0567	0,0623	0,0565
14103	HELD_FEM_UEFF	0,0371	0;0337	0,0117	0,495	0,5329	0,4948
14129	HELD_ALL_ADR3ULN	0,0605	0,0655	0,0291	0,0747	0,0807	0,076
14129	HELD_MAL_ADR3ULN	0,0384	0,0376	0,0479	0,1413	0,1647	0,1434
14326		0,0448	0,04	0,0567	0,3415	0,4056	0,3453
14503	HELD_FEM_EFF	0,1463	0,1445	0,1434	0,0461	0,0471	0,0457
14503	HELD ALL ADDRESSED	0,0052	0,0046	0,0021	0,6567	0,7349	0,6547
14503	HELD_ALL_ADR3ULN	0,0046	0,0045	0,004	0,5974	0,6922	0,5986
4503	HELD_FEM_ADR5ULN	0,0136	0,0123	0,0063	0,9862	1	0,9862
4537	HELD_FEM_ADR3ULN	0,0203	0,0189	0,0179	0,482	0,5051	0,4834
4537	HELD_ALL_ADR	0,0148	0,0153	0,0133	0,0049	0,0053	0,0048
5915	HELD_FEM_ADR .	0,0395	0,0398	0,0332	0,0288	0,0309	0,0284
5915	HELD_FEM_ADR	0,0018	0,0013	0,0012	0,6403	0,6575	0,6405
	HELD_ALL_ADR	0,0037	0,0031	0,0029	0,4718	0,5008	0,4719
5915	HELD_ALL_ADRIULN	0,1292	0,1365	0,0778	0,0267	0,0357	0,021

	P: COMPARISON	GPV.	L CTYP L XBVX	GTYPI LRPVA	ALUEL		CHALLEC
19289	HELD_MAL_CC	0,0256	mile of 411112 354	The first of the first of the first	Chi ma Sistem See See	持可能学的情報	地名自由中华人
19289	HELD_ALL_CC	0,0392					0,1642
19289	HELD_MAL_LIP	0,0974			0,0989	0,1133	0,095
36958	HELD_MAL_ADR3ULN		1	0,0242		0,0689	0,0515
37158	HELD_ALL_ADR	0,0266	1		0,0926	0,1218	0,0274
37158	HELD_FEM_ADR	0,0547		0,0248	0,0076	0,0078	0,0074
37160	HELD_FEM_UEFF	0,0494	0,0311	0,047	0,0328	0,0384	0,0323
37412	HELD_FEM_ADRSULN	1	0,0301	0,0291	0,0206	0,0238	0,0215
37412	HELD_ALL_ADRSULN	1		. 0,0228	0,0901	0,1029	0,0965
37412	HELD_FEM_ADR3ULN		0,0416	0,0443	0,1444	0,1838	0,1518
37457	CVD ALL	0,006	0,1374	0,1428	0,0436	0,0523	0,0457
37457	CVD_FEM	<b> </b>	0,0043	0,0045	0,0004	0,0006	0,0005
37457	CVD_MAL	0,0618	0,0475	0,0371	0,0084	0,0138	0,0049
37704	HELD_MAL_ADRSULN	0,1106	. 0,1397	0,1478	0,0425	0,0646	0,0633
38959	CVD_ALL	0,0093	0,1304	0,041	0,0096	0,1304	0,0423
38959	HELD_FEM_EFF	0,0357	0,0284	0,0234	0,7204	0,8145	0,7186
39292		0,0937	0,0903	0,0433	0,1155	0,1245	0,1149
39292	HELD_FÉM_ADR5ULN	0,0461	0,0797	0,1143	0,0295	0,0406	0,0445
39698	HELD_ALL_ADRSULN	0,2107	0,197	0,2673	0,0487	0,0566	0,0656
	HELD_MAL_ADRIULN	0,0549	0,0575	0,0339	0,1964	0,2316	0,1955
39756	HELD_FEM_ADR3ULN	0,1838	0,1894	0,1779	0,0494	0,069	0,0449
39951	HELD_MAL_ADR	0,0126	0,0133	0,0027	0,1824	0,227	0,1816
39951	HELD_ALL_ADR	0,0036	0,0033	0,0031	0,7179	0,7614	0,7178
39951	HELD_FEM_ADR	0,0243	0,023	0,0233	0,0941	0,102	0,0932
39951	HELD_FEM_ADR5ULN	0,0673	0,0646	0,0583	0,0366	0,0423	0,0421
40466	HELD_FEM_EFF	0,0024	0,002	0,0009	0,0045	0,0058	0,0044
40466	HELD_FEM_UEFF	0,0802	0,0728	0,0265	0,0419	0,0518	0,0382
40466	HELD_FEM_VEFF	0,0511	0,0458	0,0386	0,0313	0,0339	0,0309
44442	HELD_MAL_ADR5ULN	0,0836	0,079	0,0743	0,0364	0,0585	
55504	HELD_MAL_ADR	0,0719	0,0735	0,0691	0,0286	0,0345	0,0418
55542	HELD_FEM_ADR	0,0351	0,0377	0,0327	0,0223		0,0284
55670	LICI D		0,0252	0,0172	0,0225	0,0271	0,0221
55736	WELD ATT		0,0583	0,0098		0,03	0,0208
				2,0078	0,0205	0,0356	0,0023

	SNP COMPARISO		TO PARTICIPATE OF THE	PDICT			ALLI	LE ALI	FLE	ALLE
557	36 HELD_MAL_ADR	机路线			VAL LR	PVAL			VAL	LRPV
557	MULL					0194	0,090	Section 1	202	0,020
5574					1 1	1534	0,116		053	0,038
5581	LAND TARKE MOR				_ 1 -	412	0,13		136	0,046
5584					, , ,	867	0,023			0,023
5584			0,02			254	0,012	1 .		0,012
5584			0,095			453	0,043	2 0,06	19	0,037
5592	HELD_FEM_AD		0,137		1 -,	358	0,045			0,0453
55923	ADTEM_AD		0,058			556	0,0191	1		0,0187
55945	- LIVI_ADR3		0,060		., -,-,	559	0,0213		1	0,0222
55945	ADNEW_AD		0,0125			12	0,0031	_	ļ	0,003
55945	HELD_ALL_ADI		0,0381	-,,		42	0,0127			0,0137
56007			0,0809			82	0,0292	0,032		0,0137
56007	HELD_MAL_ADRSU	JLN	0,0308	- 7000		)5	0,1915	0,210		0,1828
56011	HELD_ALL_ADRSU		0,139	0,147	{}	56	0,2654.	4		0,2514
56104	HELD_FEM_UEF		0,1056		-,	22	0,1135	0,227		0,0343
56113	HELD_ALL_ADRSU					9	0,0164	0,019		0,0166 0,0352 0,3228
56113	HELD_ALL_ADR3U			0,0163	0,026	4	0,0347	0,0387		
56.113	HELD_FEM_ADR5U	LN (	0,0285	0,029	0,027	6	0,3219	0,3794		
56113	HELD_FEM_ADR3UI		),0402	0,0472	0,053	6	0,036	0,0498		0,0358
56636	HELD_FEM_ADR		,0416	0,0401	0,0432	2 (	0,1311	0,1519		0,1314
56636	HELD_FEM_ADR3UL		,0108	0,0106	0,0098	3 (	),5577	0,6169		0,5576
56636	HELD_FEM_ADR5UL	יט אי	,0227	0,0223	0,0215	0	,7019	0,7532		0,7016
56666	HELD_MAL_ADR3UL	_		0,0247	0,027	0	,8077	0,8498		),8079
56666	HELD_MAL_ADRSUL	14   0,	2121	0,3446	0,0763	0	,0154	0,0133		,0018
6666	HELD_MAL_ADR		3794	0,418	0,1913	0,	0556	0,0716		,0122
6667	HELD_FEM_EFF		1717	0,119	0,136	0,	0173	0,0265	<del></del>	0154
6667	HELD_MAL_ADRIULN			0,0372	0,0356	0,	0134	0,014	4	0133
6667	HELD_FEM_ADR3ULN	N   0,2		0,4124	0,2471	0,0	0382	0,0579	<del></del>	0311
6780	HELD_FEM_ADR3ULN			0,1267	0,1124	0,0	0483	0,0586	<del></del>	0492
5780	HELD_FEM_ADR			0,0159	0,008	0,	012	0,0164	<del> </del>	01.17
	HELD_ALL_ADRIULN	0,0		,0214	0,0192	0,	012	-0,0154-	<del> </del>	) <del>                                      </del>
	THE ADESULN	0,0	269 0	.0274	0,019	<del> </del>	143	0,0182	0,0	

BAYSNE				CIVEL	<b>建和特别以近天平</b> 多大位置	AUSTRALIS	ALLELE
<b>阿斯斯斯</b>		12071-00	XPVAI	LRPVAL	CPVAE	XPVAL	<b>ERPVAL</b>
56780	HELD_ALL_ADR	0,0842	0,0843	0,0808	0,0435	0,0453	0,0433
56876	HELD_FEM_UEFF	0,0372	0,0266	0,0308	0,0169	0,0232	0,0141
56876	HELD_FEM_EFF	0,0424	0,0386	0,0418	0,0166	0,0177	0,0163
56876	HELD_FEM_VEFF	0,0713	0,0569	0,0692	0,0196	0,0216	0.0192
56978	HELD_ALL_ADRSULN	0,0719	0,0767	0,0535	0,0154	0,0156	0,0118
57000	HELD_FEM_VEFF	0,0174	0,0176	0,0169	0,3734	0,4158	0,3731
57000	HELD_FEM_UEFF	0,0415	0,0406	0,0369	0,858	0,8914	0,8579
57000	CVD_ALL .	0,0418	0,0488	0,0445	0,0607	0,0713	0,0637
57000	CVD_MAL	0,0441	0,0754	0,0552	0,1657	0,2666	0,1782
57313	HELD_FEM_UEFF	0,034	0,0307	0,0344	0,1193	0,15	0,1201
57734	HELD_FEM_ADR3ULN	0,1496	0,1859	0,1593	0,0475	0,0622	0,0534
57837	HELD_MAL_ADR3ULN	0,1875	0,2505	0,1226	0,0606	0,0663	0,0405
57853	HELD_FEM_RFF	0,0026	0,0022	0,0012	0,0086	0,0107	0,0084
57853	HELD_FEM_UEFF	0,0504	0,0448	0,0138	0,0301	0,0444	0,0274
57853	HELD_FEM_VEFF	0,042	0,0386	0,0288	0,0505	0,0562	0,0501
57854	HELD_FEM_EFF	0,0212	0,0209	0,0157	0,0665	0,0761	0,0663
57854	HELD_FEM_UEFF	0,0736	0,0661	0,0242	0,0496	0,068	0,0464
57854	HELD_MAL_ADR3ULN	0,1957	0,2011	0,1232	0,0634	0,0859	0,0467
58295	HELD_MAL_ADR	0,0215	0,0221	0,0192	0,0596	0,0793	0,0593
58402	HELD_MAL_ADR3ULN	0,253	0,3601	0,2207	0,0277	0,0317	0,0255
58407	HELD_FEM_VEFF	0,009	0,0089	0,0086	0,6756	0,7344	0,6756
58407	HELD_FEM_UEFF	0,0269	0,0254	0,019	0,1833	0,1983	0.1819
58440	HELD_FEM_UEFF	0,1021	0,1012	0,1022	0,0294	0,0358	0,0305
58525	HELD_FEM_ADR	0,0008	0,0004	0,0004	0,0002	0,0003	0,0001
58525	HELD_FEM_ADR3ULN	0,0005	0,0002	0,0008	0,0002	0,0006	0,0005
58525	HELD_FEM_ADRSULN	0,0002	0,0005	0,0011	0,0009	0,0042	0,0034
58525	HELD_ALL_ADR	0,0309	0,0274	0,0284	0,0041	0,005	0,0037
58525	HELD_ALL_ADRSULN	0,0115	0,0352	0,0209	0,0263	0,0423	0,0412
58525	HELD_ALL_ADR3ULN	0,0304	0,0391	0,0408	0,0158	0,0198	0,021
58533	HELD_FEM_ADR	0,0132	0,0076	0,011	0,0024	0,0033	0,0019
58533	HELD_FEM_ADR3ULN	0,0373	0,0325	0,0534	0,0101	0,0153	0,0019
<u>5853</u> 3	HELD_FEM_ADRSULN	0,0255	0,0368	0,0556	0,0387	0,0613	0,0658
•			l		-,,	0,0013	0,0036

BAYSNP	COMPARISON			GDYRE	ALCELE	ALLELE	ALLELE
59572			CAPICOLITY OF EACH	LRPVAE	CPVAL	XPVAL	LRPVAL
58533	HELD_ALL_ADR	0,1948	0,2046	0,1921	0,0446	0,0584	0,0438
58544	HELD_MAL_ADRSULN	1	0,1955	0,0875	0,0754	0,1197	0,02
58716	HELD_MAL_ADR3ULN	0,0222	0,0288	0,011	0,0012	0,0018	0,0003
58716	HELD_MAL_ADR5ULN	0,1918	0,256	0,1602	0,0649	0,0886	0,047
58736	HELD_FEM_EFF	0,0378	0,0385	0,0374	0,0117	0,0131	0,0117
58808	HELD_FEM_ADR	0,0754	0,076	0,0739	0,0276	0,0333	0,0275
58809	HELD_MAL_ADR5ULN	0,1338	0,1368	0,0404	0,0454	0,0777	0,0088
58809	HELD_ALL_ADR3ULN	0,0117	0,011	0,0202	0,0915	0,1137	0,099
58809	HELD_MAL_ADR3ULN	0,0206	0,0207	0,0247	0,2401	0,3238	
58809	HELD_FEM_UEFF	0,1023	0,1072	0,0586	0,0482	0,0528	0,253
58886	HELD_FEM_ADR3ULN	0,0432	0,0444	0,0387	0,0115		0,0446
58886	HELD_ALL_ADR3ULN	0,0611	0,0627	0,0549		0,0145	0,0107
58886	HELD_ALL_ADRSULN	0,1212	0,1272	0,0349	0,0171	0,0233	0,0168
58926	HELD_MAL_ADR3ULN	0,0186	0,0222	<u> </u>	0,0433	0,049	0,0427
58926	HELD_ALL_ADRSULN	0,0504	0,0222	0,0152	0,0031	0,005	0,0036
58926	CVD_FEM	0,0461		0,0476	0,0108	0,0121	0,0117
58926	HELD_MAL_ADRSULN		0,0455	0,0419	0,7899	0,8184	0,7899
58968	HELD_ALL_ADR5ULN	0,1263	0,1409	0,1002	0,0427	0,0517	0,0487
58968	*	0,0212	0,0248	0,0199	0,0023	0,003	0,003
58968	HELD_MAL_ADR3ULN	0,0412	0,0375	0,0377	0,0067	0,0098	0,0085
58968	HELD_ALL_ADR3ULN	0,1321	0,1309	0,1338	0,0208	0,028	0,0226
	HELD_FEM_ADR5ULN	0,1447	0,1579	0,1408	0,0233	0,0292	0,0261
58985	HELD_ALL_ADRSULN	0,0341	0,0303	0,0449	0,0085	0,0129	0,0104
59113	HELD_MAL_ADRSULN	0,0156	0,0224	0,0114	0,0006	0,0008	0,0003
59113	HELD_MAL_ADR3ULN	0,0577	0,0875	0,0558	0,0073	0,009	0,0068
59236	HELD_ALL_ADR	0,0163	0,0158	0,0148	0,0638	0,077	0,0636
59236	HELD_ALL_ADR3ULN	0,0152	0,0151	0,017	0,3664	0,3858	0,3685
59236	HELD_FEM_ADR	0,0242	0,0266	0,0221	0,0693	0,0722	0,0689
59237	HELD_FEM_VEFF	0,021	0,0197	0.0205	0,9766	1	
59237	HELD_FEM_EFF	0,0278	0,0283	0,0273	0,5742		0,9766
59267	HELD_FEM_UEFF	0,0007	0,0006	0,0005	0,0035	0,6002	0,5742
59352	HELD MAL ADR	0,0234	0,0233	0,0219		0,0042	0,0036
59352	HELD_ALL_ADR		0,0412	0,0406	0,6204	0,6787	0,6203
···			-,0 112	V,U4U0	0,8742	0,925	0,8742

BAYSNE	COMPARISON	NAME OF TAXABLE PARTY.		<b>的人们是一个人</b>	ALUET	ACLEEC XPVAL	CG Barraniaki, v.,
59363	CVD_MAL	0,0678	0,0736	0,0797	0,0336	0,0422	1,427,24,44,44
59368	HELD_FEM_ADR	0,0119	0,0127	0,0096	0,0049	0,0053	0,0351
59371	HELD_FEM_VEFF	0,0024	0,0022	0,0021	0,1509	0,1694	
59371	HELD_FEM_UEFF	0,0098	0,0099	0,0092	0,2681	0,286	0,1508
59372	HELD_MAL_ADR	0,1687	0,1722	0,1609	0,0282	0,042	0,2686
59372	HELD_MAL_ADR3ULN	0,22	0,2638	0,2592	0,0467	0,0804	0,0273
59443	HELD_ALL_ADRSULN	0,0027	0,0031	0,0018	0,366	0,4699	0,3621
59443	HELD_MAL_ADR5ULN	0,0416	0,036	0,0368	0,877	1	0,3021
900080	HELD_FEM_ADR3ULN	0,0248	0,0243	0,0334	0,0078	0,0122	0,011
900080	HELD_FEM_ADRSULN	0,0307	0,0334	0,0528	0,0422	0,0571	
. 900102	HELD_FEM_UEFF	0,0079	0,0078	0,008	0,0043	0,0057	0,0639
900102	HELD_FEM_VEFF	0,0423	0,0413	0,0416	0,0163	0,0037	
900111	HELD_FEM_UEFF	0,022	0,0232	0,0222	0,0107	0,0103	0,0162
900111	HELD_FEM_VEFF	0,0524	0,0496	0,0516	0,0293	0,0351	0,0292
900117	HELD_MAL_LIP	0,049	0,0534	0,022	0,0073	0,033,1	0,0292
900118	HELD_FEM_EFF	0,0013	0,0008	0,001	0,0001	0,0002	0,0043
900118	HELD_FEM_VEFF	0,1013	0,0874	0,0978	0,0214	0,0303	0,0206
900118	HELD_FEM_ADR5ULN	0,0424	0,0506	0,0251	0,8579	1	
900118	HELD_ALL_ADR5ULN	0,0702	0,0623	0,0401	0,653	0,7517	0,8561
900120	HELD_FEM_EFF	0,0101	0,0092	0,007	0,0095	0,0109	0,6608
900121	HELD_FEM_EFF	0,0944	0,0944	0,0922	0,0477	0,0488	0,0093
900123	HELD_ALL_ADR	0,0402	0,0568	0,0164	0,041	0,0576	0,0476
900123	HELD_FEM_ADR	0,0678	0,1074	0,0341	0,0695	0,1089	0,0168
900124	HELD_FEM_EFF	0,0185	0,0181	0,0177	0,0602		0,0349
900132	HELD_FEM_ADR	0,0215	0,0178	0,0068	0,2283	0,0663	0,0601
900144	CVD_FEM	0,0319	0,0744	0,0093	0,0361	0,2679	0,2288
900144	HELD_ALL_ADR5ULN	0,1356	0,2119	0,0476	0,1425	0,0813	0,0104
900145	CVD_FEM	0,0702	0,0367	0,0231	0,4142	0,2202	0,0497
900145	HELD_ALL_ADRSULN	0,1364	0,2117	0,0481	0,1436	0,4698	0,4044
900146	HELD_FEM_ADR5ULN	0,0096	0,017	0,0195	0,0366	0,2203	0,0504
900146	HELD_FEM_CC	0,0751	0,0844	0,0429	0,0300	0,0413	0,0447
900146	HELD_MAL_ADR	0,1074	0,1347	0,0497		0,4606	0,4405
<u> </u>				0,0437	0,2672	0,3098	0,2671

BAYSNE	SYCOMPARISON STATES	<b>CTYPE</b>	CTYPE	CIVPE	AELDED	ALLELE	ALLEEE
		(CIV)	XPV/	TREVAL	CPVAL	XPVAL	LRPVAL
900147	HELD_ALL_ADR3ULN	0,0572	0,0567	0,0416	0,0133	0,015	0,0104
900147	HELD_FEM_ADR3ULN	0,0435	0,0527	0,0381	0,0166	0,0182	0,0127
900196	HELD_MAL_LIP	0,04	0,0376	0,0365	0,0037	0,0057	0,0039
900196	HELD_FEM_LIP	0,0183	0,019	0,0214	0,0168	0,0301	0,0136
900196	HELD_FEM_ADR3ULN	0,0672	0,0693	0,022	0,0238	0,0276	0,0198
900196	CVD_FEM	0,0398	0,0432	0,0293	1	1	1
900196	CVD_ALL	0,0617	0,0655	0,0425	0,1649	0,2139	0,1618
900200	CVD_FEM	0,0865	0,0948	0,0822	0,0359	0,0545	0,0381
900204	HELD_FEM_EFF	0,0051	0,0054	0,005	0,0195	0,0204	0,0194
900205	HELD_FEM_EFF	0,0128	0,0126	0,0126	0,0746	0,0753	0,0745
900205	CVD_MAL	0,0881	0,0873	0,0279	0,0497	0,0672	0,045
900223	HELD_FEM_ADR	0,1823	0,2018	0,1522	0,0357	0,0826	0,0327
900225	HELD_ALL_ADRSULN	0,0532	0,0765	0,011	0,0615	0,0864	0,0125
900225	HELD_MAL_ADR3ULN	0,0804	0,108	0,0242	0,0926	0,1218	0,0274
900227	HELD_FEM_ADR5ULN	0,076	0,0933	0,0368	0,0271	0,031	0,0108
900233	HELD_FEM_ADRIULN	0,0314	0,0303	0,024	0,3185	0,3387	0,3136
900236	HELD_FEM_ADR3ULN	0,0378	0,0275	0,0387	0,0494	0,064	0,0568
900236	HELD_MAL_ADRSULN	0,2375	0,2927	0,0919	0,0994	0,13	0,0289
900241	HELD_FEM_EFF	0,0225	0,0223	0,0219	0,6377	0,6538	0,6376
900242	HELD_ALL_ADRSULN	0,0164	0,0165	0,0012	0,0015	0,0017	0
900242	HELD_ALL_ADR3ULN	0,0158	0,0151	0,0031	0,0007	0,0006	0,0002
900242	HELD_FEM_ADR5ULN	0,0257	0,0467	0,0032	0,0088	0,0105	0,0007
900242	HELD_MAL_ADRJULN	0,1963	0,3073	0,0673	0,0132	0,0144	0,0014
900242	HELD_FEM_ADR	0,0219	0,0117	0,0142	0,006	0,0067	0,0053
900242	HELD_FEM_ADRIULN	0,0542	0,0556	0,0305	0,0161	0,0247	0,0091
900242	HELD_ALL_ADR	0,0373	0,0359	0,0352	0,0146	0,0152	0,0142
900242	HELD_MAL_ADRSULN	0,416	0,4311	0,2189	0,0691	0,1332	0,0142

<u>Table 6a</u> Correlation of genotypes of PA SNPs to relative risk

For diagnostic conclusions to be drawn from genotyping a particular patient we calculated the relative risk RR1, RR2, RR3 for the three possible genotypes of each SNP. Given the genotype frequencies as

	gtype1	gtype2	gtype3
case	NII	N12	N13
control	N21	N22	N23

we calculate

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$$RR1 = \frac{N11}{N21} / \frac{N12 + N13}{N22 + N23}$$

$$RR2 = \frac{N12}{N22} / \frac{N11 + N13}{N21 + N23}$$

$$RR3 = \frac{N13}{N23} / \frac{N11 + N12}{N21 + N22}$$

Here, the case and control populations represent any case-control-group pair, or bad(case)-good(control)-group pair, respectively (due to their increased response to statins, 'high responders' are treated as a case cohort, whereas 'low responders' are treated as the respective control cohort). A value RR1>1, RR2>1, and RR3>1 indicates an increased risk for individuals carrying genotype 1, genotype 2, and genotype 3, respectively. For example, RR1=3 indicates a 3-fold risk of an individual carrying genotype 1 as compared to individuals carrying genotype 2 or 3 (a detailed description of relative risk calculation and statistics can be found in (Biostatistics, L. D. Fisher and G. van Belle, Wiley Interscience 1993)). The baySNP number refers to an internal numbering of the PA SNPs and can be found in the sequence listing, null: not defined.

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In cases where a relative risk is not given in the table (three times zero or null) the informative genotype can be drawn from the right part of the table where the frequencies of genotypes are given in the cases and control cohorts. For example BaySNP 3360 gave the following results:

BAYSNE GOVEARISON	STEPH	CIYPL2	GTYPE3	RRI	RR2	RR3
3360 HELD_MAL_ADRSULN	GG	GJ.	TT	null	0	0.

FOLA	FQ2.A.	TO SAX	TOLK	FQ2-B	FQ3_B
10	0	0	50	22	I

It can be concluded that a GT or TT genotype is only present in the control cohort; these genotypes are somehow protective against ADR. An analogous proceeding can be used to determine protective alleles if no relative risk is given (table 6b).

12.02         78         REGORE           60         78         80           40         131         125           76         114         119           44         39         57           16         25         29           31         22         30           17         27         41           19         337         512           9         54         71           21         119         151           22         56         97           3         56         97           3         56         97           3         56         97           3         56         97           3         56         97           5         124         219           5         124         219           5         130         224           5         130         224           1         59         102           1         129         196	31 19 129 196 19 15 58 86
60 78 60 78 40 131 76 114 44 39 16 25 16 25 17 22 19 337 19 34 10 34 11 119 2 124 2 124 2 124 2 124 2 56 3 56 3 56 4 56 6 56 7 56 8 56 8 56 8 56 8 56 8 56 8 56 8 78 8 78 8 8 78 8 78	15
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IREQ2:A	95	85	24	44	28	0	0	16	10	31	14	17 .	.99	17	102	17	58	4	32	41	. 91	19	-
RROTS	146	123	38	162	118	200	162	120	30	57	12	21	126	45	106	- 51	86	12	56	. 151	72	119	1
SIZE	101	<u>\$</u>	31	103	73	8	82	89 .	82	4	13	19	96	31 .	104	34	28	00	4	96	4	69	1
RR	1,22	0,89	89'0	1,25	1,28	0	0	9,0	0,16	1,53	2,12	1,92	52,1	1,44	1,22	0,63	1,24	0,78	1,43	0,78	99'0	0,87	1
RRO	0,82	1,13	1,47	8,0	0,78	冒	賣	1,57	6,2	59'0	0,47	0,52	8,0	69'0	0,82	1,58	0,81	1,28	120	1,28	1,52 0	1,15	
COMPARISON	1	CVD_ALL	HBLD_FEM_CC	· CVD_ALL	HELD_FEM_ADR	HELD_ALL_LIP	HELD_FEM_LIP	CVD_MAL	HELD_MAL_HDL	HELD_ALL_CC	HELD_MAL_CC	HELD_MAL_LIP	CVD_ALL	HELD_FEM_CC	. CVD_ALL	HELD_ALL_HDL	HELD_FEM_LIP	HELD_MAL_ADRSULN	HELD_MAL_CC2	HELD_ALL_LIP 1	HELD_ALL_CC 1	. CVD_MAL 1	
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y azis	4	45	62	39	624	0g.	17	43	237	46	119	19	53	58	6	30	89	99	132	91	47	98	1
III	2,4	1,38	0,45	9,0	88,0	69'0	1,75	0,46	0,77	0,62	0,74	0,26	0,73	89'0	2,7	1,54	0,14	II DIL	0,46	lina Ina	0,34	1,35	
B	0,42	0,73	2,22	1,68	<u>1.</u>	1,46	0,57	2,15	E.	19,1	1,35	3,89	1,37	1,47	0,37	0,65	7,27.	0	2,19	0	2,97 0	0,74	
COMPARISON	HELD_MAL_CC	HELD_AIL_CC	HELD_WAL_HDL	HELD_ALL_FIDI	HELD_ALL_LIP2	HELD_FEM_LIP	HELD_MAL_LP	HELD_FEM_UEFF	HELD_FEM_EFF	HELD_MAL_ADR	HELD FEM VEFF	HELD_MAL_ADR3ULN	HELD FEM UEFF	HELD MAL ADR	HELD_MAL_ADRSULN 0	HELD_FEM_ADR3ULN 0	HELD_FEM_ADR 7	HELD FEM ADRULN	HELD_ALL_ADR 2	HELD_FEM_ADRSULN	HELD_ALL_ADR3ULN 2	HELD_FEM_LIP 0,	
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leganori, na	128	71	: 5	3 %	3 8	8	32	18	.02	=	22	249	117		æ :	178	58	527	1193	76	66	3	225	-	
ROTE INTO STATE AN	8	. 13	11	=	; ;	14	11	4	85	6	13	270	99	1	45	<u>8</u>	31	630	620	52	4	30	307	22	-
RIC	1.25	2.17	0.42	1.55	9	82'0	0,28	2,41	8,0	0,64	0,59	E	1,36	.   5	70'n	1,29	59'0	1:1	1,26	15,1	60'0	0.12	1.04		4
THE R	25	0,46	2.4	790		-	3,58	0,42	1,24	1,57	1,68	60	0,74		70,1	0,77	1,54	16,0	0,79	0,77	11,29 0	8,33 0			
CONPARISON	HELD_ALL_LP	· HELD MAL CC	CVD FEM	HELD FEM CC	HELD MAI CC	יייייייייייייייייייייייייייייייייייייי	HELD_MAL_LIP	HELD_MAL_CC	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_MAL_ADR3ULN	HELD_FEM_BFF	CVD_MAL	۶		CVD_ALL 0	HBLD_FEM_CC 1	HELD_ALL_LIP2 0	HELD_ALL_LP2 0	HELD_FEM_UEFF 0	HELD_ALL_CC 11	HELD FEM CC 8		+	7
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BAYSAR KALTERER ABORDE	Į-,	Ö	Ð	A	¥	,	5	A	A	¥	¥	A	A	¥		€	¥	Ą	၁	£-	H	٤	1	A	
BAYSIN	2203	2217	2217	2281	2281	7367	5977	2290	7327	2327	2327	1327	2353	2353	1353	CCC7	2353	2371	23.76	2401	2463	2463	2463	2755	

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FREO2 B	94	235	156	88	13	001	53	0	5	53	17	24	17	0	0	0	17	10	62	7	26	103	
IIR O FB	162	333	134	99	49	116	231	120	31	49	71	156	7.1	126	09	99	17	20	. 84	141	46	161	1
Sizes	128	284	145	11	31	108	142	99	<u>82</u>	51	44	8.	44	63	Ŕ	33	17	15	55	74	36	132	1
FREOMA SIZE B	121	211	119	44	. 2	89	49	-	-	33	14	-	1	10	7	3	14	13	88	17	9	49	
Mioaud vazis ou	147	331	163	22	32	125	253	17	55	. 25	0	35	23	190	129	19	32 .	11	76	16	30	47	1
V azis	134	271	141	\$2	17	107	151	6	28	. 45	7	18	12	100	88	32	23	12	53	\$4	82	48	
M.	1,18	26,0	0,79	89'0	0,34	16'0	0,92	8,06	0,26	17,0	Hon	0,22	6,23	1,66	1,47	2,08	69'0	1,59	69'0	1,81	0,47	1,43	1
	0,85	1,05	1,27	1,48	2,96	13	1,09	0,12	38,	4.	0	4,58	4.	9,0	89.0	0,48	1,45	6,63	1,46	0,55	2,11	7,0	
CONTACTOR	HELD_ALL_ADR	HELD FIM BFF	HELD_REM_VEFF	HELD_FEM_UEFF	HELD_FEM_ADR3ULN	HELD_FEM_VEFF	HELD FEM VEFF	HELD_MAL_ADRSULN	HELD_FEM_CC	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_ALL_ADRSULN	HELD_MAL_ADR3ULN	CVD_ALL	CVD_MAL	CVD_FEM	HELD_MAI_CC2	HELD_FEM_HDL	HELD_FEM_UEFF	HELD_FEM_UEFF	HELD MAL LIP	HELD_ALL_ADR3ULN	
Volence	ά	ß	¥	¥	A	A	ຶ	ຽ	ŋ	Ü	A	Ą	∢ .	ဗ	g	ŋ	٤	· <u>F</u>	Ŧ	¥	ပ	F-	
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	1755	55	25	25	43	52	14	15	17	-	9	9	9	2	2	2	3	8	<u> </u>	~			_
BA ST	77	7755	2925	2925	3043	3152	3214	3215	3237	3241	9286	3826	3826	3842	3842	3842	3843	3843	3869	3942	4018	4206	

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Krakelani	89	191	80	546	30	36	202	97	202	- 26	97	201	201	. 60	, 6	101	130	60	25	F 3	501	co.	3
SIZER	2	132	\$2	370	16	. 29	124	71	124	\$5	55	130	<u>6</u>	9	3 8	32	3 2	1 2	2 2	5 2	3 9	3 6	-
FREO2 A	22	28	78	132	7	. 61	28	\$	16	. 4	37	83	31	14	3.1	: 82	) <u>«</u>	×	2 9	5   2		. 08	6
ARCHARO SIZE A CREDITA	72	24	114	208	17	7.1	89	162	36	20	87	183	83	20	885	181	34	474	38	200	15	113	-
SIZEK	72	97	17	320	12	\$	48	104	56	-12	79	133	47	12	19	132 .	56	286	81	17	6		:
THE STATE OF	1,27	1,65	0,85	0,84	2,15	0,2	1,5	18,0	1,71	2,34	55,	1,23	4,	2,34	1.37	1,22	99'0	1.17	0.7	1,62	131	0.83	
W.	0,79	19'0	1,18	1,19	0,47	1,43	290	1,24	65,0	0,43	0,74	0,82	69,0	0,43	0,73		1,52	0,85	1,44		<del> </del> -	<del>` ∤ ∸</del>	⊣
COMPANISON	HELD_FEM_ADR	HELD_ALL_ADRSULN	CVD_ALL	HELD_FEM_LIP?	HELD_MAL_CC	HELD_MAL_CC2	HELD_ALL_ADR3UIN	HELD_ALL_CC2	HELD_ALL_ADRSULN	HELD_MAL_ADR3ULN	HELD_MAL_ADR	HELD_ALL_ADR	HELD_ALL_ADR3ULN (	HELD_MAL_ADR3ULN 0	HELD MAL ADR 0	HELD_ALL_ADR 0	HELD_ALL_ADRSULN 1	+-	HELD MAL LIP	HELD MAL LIP 0	HELD_MAL_ADRSULN 0,	HELD ALL CC2	7
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BAYSNE	4206	4206	. 4527	4527	4527	4527	4527	4527	4527	4544	4544	4544	4244	4545	4545	4545	4668	4669	4718	4818	4827	4838	

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KREO2	3	76	78	13	23	78	Ξ	19	19	Ξ	19	E	Ξ	9	99	Ξ	34	8	16	গ্ৰ	8	24	
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SIZE B	34	ė\$	59,	18	38	31	128	69	69	128	69	128	128	20	70	128	8	59	21	34	62	22	
FREO? A	.138	36	5	2	15	17	45	33	21	30	78	135	44	32	20	29	6	54	35	33	78	6	
SIZE A EREGIS	0	88	=	26	75	7	51.	29	13	22	89	135	25	30	14	23	27	89	. 25	25	96	27	
V IIIS	69	62	∞	4	45	12	48	31	17	26	73	135	48	31	17	56	18	19	30	32	87	18	
RRO	Ina	1,19	1,51	0,25	29'0	2,21	1;1	1,28	1,77	1,62	1,2	1,14	1,08	1,28	1,68	15,1	0,47	0,81	1,4	1,66	0,82	0,47	1
RR	0	0,84	99'0	3,98	1,48	0,45	66	0,78	95'0	0,62	9,84	88.0	6,9	0,78	9,0	99,0	2,11	1,24	17,0	9,0	1,21	2,11	İ
UR COMPARISON	CVD_MAL	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_MAL_CC	HELD_ALL_CC	HELD_MAL_LIP	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_FEM_ADR	HELD_ALL_ADR	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_MAL_LIP	HELD_MAL_ADR	HELD_FEM_CC	CVD_FEM	HELD_ALL_CC2.	HELD_MAL_HDL	
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BAYSIN	4856	4868	4868	4887	4887	4912	4951	4951	4951	4951	4951	4951	4952	4952	4952	4952	4966	9961	4966	5019	6105	5019	-

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FREO	ጽ	4	46	A !		911	24	0.5	757	4	2 2		67	42	27	30		2	88	26	104	7	6	73	. 51	37
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	0,75	7,0	1.6	3	10,1	1,21	1,87	2,35	1.29	190	. 2	250	3 1	0,47	0,25	0.53	27.77	3	0,84	0,36	0.67	160	-	1	0,18	0,48
والمبدوب	1,33	1,43	0.63	27.0	2,	0,82	0,53	0,42	0,77	5	0.83	<del> </del> -		2,13	4,08	1,88	0 110	+	1,19	2,75 0	1,49	┿~		<del>- i</del>	5,56 0,	2,07 0,
	יום באל מאטוי	HELD_MAL_CC2	HELD FEM ADR3ULN	HELD MAT ADREITM	William China	neLU_rem_ADR	HELD_FEM_ADRSULN	HELD_MAL_ADRSULN	HELD_FEM_VEFF	CVD FEM	HELD FEM VEFF	2	<del> -</del>	NTO CATE TO A	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN 1	HELD MAL ADRSULN			HELD_FEM_ADRSULN 2	HELD_MAL_ADR 1	HELD FEM ADRSULN	-	$\dashv$	WAL AURSULN	HELD ALL ADRSULN   2,
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5019	0.03	SINC	5165	5165	5165	5715	COTO	5278	. 5287	5320	5324	5373	5373	5275		5375	5376	5377		1/50	5517	5518	5564	5569	6955	

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m.com	92	. ES	92	53	122	91	6	28	33	<b>E9</b>	20	43	20	20	55	64	75	37	9	15	7	10
TREO! B	126	99	126	65	142	22	21	30	83	193	112	205	112	112	83	72	17.1	62 .	30	99	29	130
SILLER	109	59	109	53	132	61	5.	29	58	128	98	124	99	99	72	89	126	28	. 82	40	37	07
TREOTAL SIZE BURKOLB GROOT	54	40	28	20	-32	22	14	38	40	88	-11	13	39	81	20	4	42	. 19	28	7	15	27
INTO A	34	. 81	91	10	20	12	14	78	76.	177	21	33	105	42	54	82	52 .	ŚI	0	. 83	55	191
y aras	44	. 53	22	115	76	12	14	. S8	58	129	16	23	72	30	52	63	47	17	<u>4</u>	45	35	75
O I	1,74	1,98	2,07	2,05	1,68	29,1	1,52	8,0	1,15	1,18	2,25	1,67	1,37	1,74	1,26	77,0	1,58	2,13	E E	0,57	15,1	5,1
inu.	0,57	5,0	0,48	0,49	0,59	19'0	990	1,25	0,87	0,85	0,44	9,0	0,73	0,58	0,79	1,31	0,63	0,47	0	1,76	99'0	0,77
COMPARISON	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_ALL_ADRSULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	CVD_FEM	HELD_MAL_CC	CVD_MAL	HELD_MAL_ADR	HELD_ALL_ADR.	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_FEM_ADR	HELD_FEM_ADR3ULN	HELD_FEM_UEFF	HELD FEM LIP	HELD_ALL_ADR3ULN	HELD_MAL_ADR3ULN	HELD_MAL_CC	HELD_ALL_CC	CVD_FEM	CVD_ALL
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BAVSNP ALLIBURI KOLK	. <u>9</u>	Ģ	ტ	ָט	Ö	ອ .	Ð	ტ	υ <sub>.</sub>	Ŧ	۲	Ŀ	į-	ī	ပ	T	£.	T.	F .	E-	F	T
HAKSME	5716	5716	5716	5716	5717	5717	5850	6565	6151	6236	6277	6277	6277	6277	6313	6369	6374	6374	6396	6396	6396	6396

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COACH		37	'n	6	15	28	3 5	2   5	?	<b>90</b>	13	1	ž	2	6	80	3,4	3	m	97	13	6		7	31.	, in		;
SZEZ	140	Q£1	1	23	35	96	9	113		97	<b>\$</b>	27	č	;	127	2	246		71	:153	75.	47	; ;	39	101	25	-13	2
STLEET	88	3 ,	×	16	25	62	31	E	: :	=	31	17	84	1	13	26 ·	136	2	71	125	4	28	5	3	 99	55		-
RR2	3:		7,77	1,59	1,63	1,16	1.33	127	0.43	7 6	76'7	3,89	227	3	7/1	2,67	1,38	272	<u>}</u>	1,05	0,48	0.47	. 10	2	0,76	9.44	E.	+
RR	0.76	6	76'0	0,63	0,61	98,0	0.75	0.79	226		45.0	0,26	14,0			0,37	0,72	170	-	0,95	2,09 0	2,11		<del>-+</del>	1,32 0	2,25 0,	-	
COMPARISON	HELD_ALL_CC2	HELD MAY ANDSTEIN	ייייי בייייי	HELD MAL ADRIULN	HELD_ALL_ADRSULN	HELD MAL ADR	HELD_FEM_ADR3ULN	+-	Z			HELD_FEM_ADRSULN (	HELD_ALL_ADR3ULN (	HELD FEW ADR	-	HELD_ALL_ADRSULN 0	HELD_ALL_ADR 0	HELD ALL CC	1		HELD_ALL_ADR3ULN 2,	HELD_FEM_ADR3ULN 2,	HELD ALL ADRITIN 2			HELD_FEM_ADRSULN 2;	HELD FEM LIP 0,77	7
Alterior	A	A	*	₹	٧	Y	. <b>4</b>	A	5	-	E	-	L	Ë	†		<b>E</b>	ပ	ر	+	T	T	T	E	1	H	Α	1
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BAYSINE	6486	6520	6520		6520	6520	6522	6522	6524	9659	y03.9	200	9659	9659	6596		0550	6734	6743	2130	0717	7128	7128	7128	7170	0711	7363	

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IRREO?	45	41	4	23	37	82	112	9	33	101	36	56	101	34	45	12	17	0	0	88	88	85
RREOLD RITHERS OF B	. 185	130	130	95	33	· 18	116	99	125	147	78	. 82	147	120	179	. 246	246	78.	89	167	191	167
SIZIEB	115	72	72	59	35	61	114	36	22	124	19	29	124	11	112	129	129	39	34	126	126	126
W. CO. W.	57	10	14	0	01	12	76	. 10	22	39	28	89	117	. 91	24	10	9	9	6	44	113	25
REC SIZE A FREDLEA	143	24	48	14	28	16	112	28	136	53	30	202	137	136	. 166	98	46	48	66	. 50	151	27
VETICS.	188	17	31	7	61	14	94	19	79	46	29	69	127.	26	95	48	26	iz	54	47	132	56
B	1,28	2,67	1,85	0	0,46	8,0	0,82	2,1	0,77	1,05	1,2	1,16	Ξ,	9,0	0,72	1,75	2,12	2,63	69,1	1,48	7.	1,63
N.	0,78	0,37	0,54	Tim	2,16	1,25	1,22	0,48	<u></u>	56,0	0,83	0,8%	60	1,66	1,38	0,57	0,47	0,38	0,59	99'0	0,83	0,61
W COMPARISON	HELD_ALL_LIP	HELD FEM ADRSULN	HELD_FEM_ADR3ULN	HELD_MAL_ADRSULN	HELD_MAL_LIP	. HELD_MAL_CC	HELD_ALL_LIP	HELD MAL LIP	HELD_FEM_LIP	HELD_ALL_ADR3ULN	HELD_FEM_ADR3ULN	HELD_FEM_ADR	HELD_ALL_ADR	HELD FEM LIP	HELD ALL LIP	HELD_ALL_ADR3ULN	HELD_ALL_ADRSULN	CVD_FEM	CVD_MAL (	HELD_ALL_ADR3ULN	HELD_ALL_ADR	HELD_ALL_ADRSULN (
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	7363	7.100	7409	7409	8138	8138	8138	8168	8168	8210	8210	8210	8210	8241	824 1	8249	8249	8480	8480	8577	8577	8577

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RRROTER	91	23	23	. 23	41	321	77	69	61	40		. 74	26	3 8	3 2	3 2	=	:   •	2	3 8	2 2	3 2	<u></u>
KKROLER	169	81	ŏ	150	187	419	. 21	78	1111	44	21	70	2 8	27.3	15	113	80	22	S 5	222	131	256	}
SIZE	130	25	52	52	417	370	22	2	65	42	17	4	55	143	9	74	8	14	. F	129	111:	145	:
ICREOS A SIZE B		7		0	∞	227	[2	. 59	46	33	14	3	2	48	2	80	4	0	S	22	2	61	
Right RRA STATE AFFIRE OF THE	. 15	87	27	14	74	403	24	121	. 138	71.	22	43	30	230	16	06	12	24	71	74	163	283	-
SIZE	48	47	14	7.	41	315	18	96	92	22	282	23	92	139	0	24	∞	12	38	84	55	151	1
RR	1,43	0,45	0,17	0	95'0	0,84	0,53	8.0	1,28	0,73	1,0,1	0,46	0,28	0,85	0,43	0,77	2,69	0	5,0	1,52	0,53	89,0	۲.
N.	0,7	2,22	9	III.	17.		<u>6,</u>	1,25	0,78	1,37	66'0	2,16 (	3,52 (	1,17	2,32 0	1,31 0	0,37 2		2	0,66	1,89 0,	1,46 0,	$\dashv$
ica - Companison		HELD_MAL_ADR	HELD_MAL_ADR3ULN	HELD_MAL_ADRSULN	HELD_ALL_ADR3UEN	HELD FEM LIP2	HELD_FEM_HDL	HELD_ALL_CC2	CVD_ALL (	HELD_FEM_CC2	HELD MAL HDL	HELD_FEM_ADR3ULN 2	HELD_MAL_ADR3ULN 3	HELD FEM VEFF	HELD_MAL_ADRSULN 2	HELD FEM UEFF 1,	HELD_MAL_ADRSULN 0	HELD_MAL_CC n	HELD_ALL_CC	HELD_ALL_ADR3ULN 0,	HELD FEM UEFF 1,	HELD FEM VEFF 1,	
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	<i>L</i> 9	39	61	2	;	======================================	81	8	243	103	637	85	314	35	19	98	140	269	82	47	47	25	313
	Ton	llun	nuli	150	3	1,89	0,75	99'0	0,85	1,22	0,89	0,74	98'0	25.0	0,54	8,0	1,2	1,14	3,07	0,79	0,74	0,52	0.84
	0	0	0	1.96		0,53	1,34	1,47	1,18	0,82	1,13	1,35	1,16	1,56	1,84	1,25	0,83	0,88	0,33	1,27	1,36	1,92	1,19 0
The state of the s	CVD_MAL	HELD_ALL_HDL	HELD MAL IDL	HELD MAL LIP	HEID MAI TEN	ACLD WAL LIP	HELD FEM LIP	CVD_MAL ·	HELD FEM LIP2	CVD_ALL	HELD_ALL_LIP2	HELD_ALL_LIP	HELD MAL LIP2	CVD_FEM	HELD_MAL_LIP	HELD FEM LIP	HELD_FEM_VEFF	HELD FEM EFF	CVD_FEM 0	HELD_ALL_ADR3ULN 1	HELD_ALL_ADR3ULN 1	HELD_ALL_ADRSULN 1	HELD_MAL_LIP2 1
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RRS			}   6	25	2,29	0,84	0,89	0.99	0	2, 0	2 3	G.	1,27	1,19	1.42		15.	0,52	0,81	986	7 43	2	7'7	1,17	1,13	1,55
RE	66,0	0.53			0,44	1,19	1,12	10	. 65	12	1 6	3	0,79	9,84	100		-	1,94	1,24	1,16	041		<u>-</u> ļ	0,86	0,88	0,64
COMPARISON	CVD_FEM	HELD MAL ADRIULN	HELD ALL 1 P2	HEI D MAI ADDONE	NAL ADKOULN	HELD_MAL_LIP2	HELD_ALL_LIP2	CVD_FBM	HELD MAL ADRIULN	HELD ALL LIP	HELD MAI. ADRUILIN	Und to make	י אוד הבעו רוזבעו	HELD_ALL_CC2	HELD FEM ADRSULN	+	-	2	HELD_ALL_ADR	HELD FEM VEFF	HELD MAL HDL	-	7	MAL_LIP2	HELD_ALL_LIP2 0,	HELD_ALL_HDL 0,
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SIZE B	89	124	94	36.	40	350	735	69	69	69	22	40	9	347	722	8	81	127	58	22	29	8	
RECORY	39	\$	26	11	6	89	128	4	9	11	15	20	33	124	230	6	9	-	3	2	12	91	
FRED.	<b>86</b>	061	62	21	59	995	1142	30	56	135	47	99	93	502	1036	81	22	16	119	52	84	74	
A SIZE A	69	127	\$	19	34	317	635	11	31	73	31	43	63	313	633	45	14	46	19	31	. 48	45	
RRZ	1,38	1,27	1,34	2,37	2,11	1,27	1,15	2,41	1,84	1,36	1,56	90,1	1,32	1,22	1,16	890	0,43	0,17	0,44	99,0	19'0	8,0	
RR	6,73	0,79	0,75	0,42	0,48	0,79	0,87	0,41	0,54	0,73	0,64	26,0	92,0	0,82	98'0	1,48	2,35	5,88	2,29	1,52	1,49	1,24	
COMPAUSON	HELD_FEM_ADR	HELD ALL ADR	HELD_ALL_CC	HELD_MAL_LIP	CVD_FEM	HELD MAL LIP2	HELD_ALL_LIP2	HELD_FEM_ADRSULN	HELD_FEM_ADR3ULN	HELD FEM ADR	HELD_FEM_CC	HELD_ALL_CC	HELD_MAL_ADR	HELD_MAL_LIP2	HELD_ALL_LIP2	HELD_ALL_CC	HELD_MAL_CC	HELD_ALL_ADR3ULN	HELD_MAL_ADR	HELD_FEM_CC	HELD_MAL_CC2	HELD_ALL_CC	
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RR	1.02	0.35	0.55	0.7.7	12,0	3	-	1,28	1,22	2,45	1,31	1,27	<del>-</del>  -	-	0	0	0	30%	<u>-</u>  -			0,47 2	1,17 0,	1.06	+-	{
COMPARISON	HELD ALL HDL	HELD_MAL_ADRSULN	_	+		1		CVD_ALL	HELD MAL ADR	HELD_FBM_CC	HELD FEM LIP	HELD_ALL_LIP	HELD MAL LIP	$\dashv$	nELL_ADKSULN	HELD_MAL_ADR3ULN	HELD_MAL_ADRSULN	HELD ALL ADRIULN 3				HELD_MAL_ADR3ULN 0;	HELD_ALL_ADRIULN 1,	HELD_ALL_ADRSULN 1.0	+-	ᆟ
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BAVSNP	11614	11631	11631	11637	11637	11637	11637		11041	11645	11646	11646	11652	11727	11999	17/71	11727	11727	11727	11728	11914		11938	11938	11938	

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TREE OF B	32	32	32	32	25	11	801	19	108	63	108	19	9 .	9	14	188	27	27	27	32	32	32
KREOLBI	78	78	78	84	127	215	144	79	144	61	4.	79	136	134	242	262	83	ಜ	83	84	84	84
SIZEB	55	55	55	. 88	92	113	126	92	126	8.	126	70	11	07.	128	140	. 55	52	55	58	88.	28
FREOZ A	16	3	<u>26</u>	14	28	4	43	21	30	31	133	76.	14	16	28	29	6	44	. 14	9	44	11
RRI RRY SIZE A VREOLA TREOZA SIZE B KREOLBI GREOZB	0	27	**	0	82	234	51	13	22	29	133	89	80	130	240	243	. 7	99	18	12	74	23
SIZEA	œ	15	55	7	55	. 119	47	17	52	30	133	72	51	22	134	136	00	55	16	6	83	17
RR	Brad	0,33	0,86	Ting.	1,35	15,0	1,09	1,81	1,64	1,25	1,15	1,2	1,78	1,48	1,34	1,28	3,21	4,1	1,92	1,26	1,24	1,19
RR	0	m	1,16	0	0,74	1,95	0,92	0,55	19'0	8,0	0,87	6,83	95'0	89'0	0,75	0,78	0,31	0,71	0,52	0,79	0,81	0,84
COMPARISON	HELD_MAI_ADRSULN	HELD_MAI_ADR3ULN	HELD_MAL_ADR	HELD_MAL_ADRSULN	HELD_FEM_UEFF	HELD_ALL_ADR	HELD_ALL_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_ADRSULN	HELD_FEM_ADR3ULN	HELD_ALL_ADR	HELD_FEM_ADR	HELD_FEM_UEFF	HELD FEM ADR	HELD_ALL_ADR	HELD_FEM_VEFF	HELD_MAL_ADRSULN	HELD_MAL_ADR	HELD_MAL_ADR3ULN	HELD_MAL_ADRSULN	HELD_MAL_ADR	HELD_MAL_ADR3ULN
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5	∞	47	26	89	12	30	2	15	36	6	bar Park	.17.	24	6	4	1.7	35	109	58	S	21
11	24	217	<b>86</b> ·	234	22	8	24	19	20	25		11	88	23	12	11	. 75	187	42	57	21
∞	16	132	29	151	17	62	17	17	\$	17	ó	47	179	91	∞	47	55	148	52	3	21
2,8	1,97	1,26	1,41	1,23	1,92	0,94	0,94	1,43	1,39	1,46	1,27	10,1	1,06	1,48	1,36	86,0	0,92	1,02	E	0,52	1,21
0,36	0,51	0,79	0,71	0,82	0,52	1,07	1,06	0,7	0,72	99,0	0.79	66,0	96,0	89,0	0,74	<del> </del>	+	<del> </del>	60	╄	95,0
HELD_MAL_ADRSULN	HELD_MAL_ADR3ULN	HELD_ALL_ADR	HELD_MAL_ADR	HELD_FEM_VEFF	HELD_FEM_ADRSULN	HELD_MAL_ADR	HELD_MAL_ADR3ULN	HELD_FEM_ADRSULN	HELD_ALL_CC	HELD_MAL_ADRIULN	THEED_MAL_ADRSUEN-	HELD_ALL_ADR3ULN	<del> </del>	-	HELD_MAL_ADRSULN	HELD_ALL_ADR3ULN	HELD FEM UEFF	HELD_FEM_VEFF	HELD_MAL_ADR	CVD_FEM	HELD_FEM_VEFF (
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	A G HELD_MAL_ADRSULN 0,36 2,8 8 11 5 60 106	A G HELD_MAL_ADRSULN 0,36 2,8 8 11 5 60 106 A G HELD_MAL_ADRSULN 0,51 1,97 16 24 8 60 106	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         -98         26         55         99           A         T         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243	A         G         HELD_MAI_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAI_ADRSULN         0,51         1,97         16         24         8         60         106           A         T         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           A         T         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115	A         G         HELD_MAI_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAI_ADR3ULN         0,51         1,97         16         24         8         60         106           A         G         HELD_ALL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           T         C         HELD_MAL_ADR         1,07         0,94         62         94         30         60         88	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         106           A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_ADRSULN         0,82         1,23         17         22         12         115         115           T         C         HELD_MAL_ADR         1,07         0,94         62         94         30         60         88           A         C         HELD_MAL_ADRSULN         1,06         0,94         17         24         10         58         80	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         T         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         C         HELD_FEM_VEFF         0,82         1,23         151         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88           A         C         HELD_FEM_ADRSULN         0,7         1,43         17         24         10         58         80	A         G         HELD_MAI_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAI_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_MAI_ADR         0,71         1,41         62         98         26         55         99           A         T         HELD_MAI_ADR         0,71         1,41         62         98         26         55         99           T         A         T         HELD_FEM_VEFF         0,82         1,23         171         234         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         17         115           A         C         HELD_MAI_ADR         1,07         0,94         62         94         30         60         88           A         C         HELD_MAI_ADRSULN         0,71         1,43         17         24         10         58         80           A         C         HELD_MAI_ADRSULN         0,71         1,43         17         24	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106           A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232           A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99           T         A         T         HELD_FEM_ADRSULN         0,72         1,23         151         224         68         144         243           T         C         HELD_FEM_ADRSULN         0,52         1,92         17         22         12         71         115           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88         9           A         C         HELD_FEM_ADRSULN         1,07         1,43         17         24         10         58         80         7           G         A         HELD_AMAL_ACC         0,72	A         G         HELD_MAL_ADRSULN         0,36         2,8         8         11         5         60         106         14           A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         14           A         A         G         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232         30           A         T         HELD_MAL_ADR         0,79         1,26         132         217         47         131         232         30           T         A         T         HELD_MAL_ADR         0,72         1,23         151         234         68         144         243         45           T         C         HELD_FEM_ADRSULN         0,52         1,23         17         22         12         115         27           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         30         60         88         36           A         C         HELD_MAL_ADRSULN         1,07         0,94         62         94         10         58         99         17 <th>  A   G   HELD_MAL_ADRSULN   0,36   2,8   8   11   5   60   106   14     A   G   HELD_ALL_ADR   0,71   1,97   16   24   8   60   106   14     A   T   HELD_ALL_ADR   0,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADR   0,71   1,41   62   98   26   55   99   11     T   C   HELD_MAL_ADR   0,71   1,71   22   12   71   115   27     T   C   HELD_MAL_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAL_ADRSULN   1,06   0,94   17   24   10   58   80   36     A   C   HELD_MAL_ADRSULN   0,7   1,43   17   19   15   70   93   47     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,99   1,27   9   77   77   77   77   77   77   7</th> <th>  A   G   HELD_MAL_ADRSULN   Q,51   1,97   16   24   8   11   5   60   106   14     A   T   HELD_ALL_ADR   Q,79   1,26   132   217   47   131   232   30     A   T   HELD_MAL_ADR   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_FAM_ADRSULN   Q,52   1,92   17   22   12   71   115   27     T   C   HELD_MAL_ADR   1,07   Q,94   62   94   30   60   88   32     A   C   HELD_FEM_ADRSULN   Q,64   1,7   24   10   58   80   36     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,9   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   77   78   79   97   21  </th> <th>0         A         Q         HELD_MAL_ADRSULN         0,51         1,87         16         24         8         11         5         60         106         14           9         A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         14           1         A         G         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADRSULN         0,72         1,72         17         22         12         71         115         27         17         14         24         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,72         1,93         17         19         15         70         99</th> <th>A         G         HELD_MAL_ADRSUIN         0,36         2,8         8         11         5         60         106         14           A         G         HELD_MAL_ADRSUIN         0,51         1,97         16         24         8         60         106         14           A         G         HELD_MAL_ADRSUIN         0,71         1,41         62         98         26         55         99         11           A         T         HELD_MAL_ADRSUIN         0,71         1,41         62         98         26         55         99         11           T         A         T         HELD_FEM_ADRSUIN         0,72         1,72         17         22         12         71         115         27           T         C         HELD_MAL_ADRSUIN         0,52         1,72         17         22         12         71         115         27           A         C         HELD_MAL_ADRSUIN         0,52         1,72         17         24         10         58         80         36           A         C         HELD_MAL_ADRSUIN         0,71         1,43         17         24         10         58         36         46&lt;</th> <th>  A   O   HELD_MAI_ADRSULN   0,36   2,8   8   11   5   60   106   14     A   O   HELD_MAI_ADRSULN   0,51   1,97   16   24   8   60   106   14     A   T   HELD_MAI_ADRSULN   0,71   1,41   62   98   26   55   99   11     A   T   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     T   C   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAI_ADRSULN   0,60   0,94   17   24   16   15   16   36   36   36     G   A   HELD_MAI_ADRSULN   0,70   1,43   17   19   15   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,43   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,47   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,47   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,70   1,71   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,71   17   17   17   17   17   17  </th> <th>A         G         HELD_MAL_ADRSULN         0,26         2,8         8         11         5         60         106         14           A         G         HELD_MAL_ADRSULN         0,79         1,26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         36         69         11           1         A         T         HELD_MAL_ADR         0,92         1,7         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         0,7         1,43         17         24         10         88         26<th>A         G         HELD_MAL_ADRSULN         0,26         2,8         8         11         5         60         106         14           9         A         G         HELD_MAL_ADRSULN         0,79         1,56         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_FEM_ADRSULN         0,72         1,72         17         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         1,03         62         94         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,71         1,43         17         24         76         <t< th=""><th>A         Q         HELD_MAL_ADRSULN         0.36         2.8         8         11         5         60         106         14           0         A         G         HELD_MAL_ADRSULN         0.79         1.26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0.71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         88         32           1         A         T         HELD_MAL_ADRSULN         0,54         17         24         10         88         32           4         C         HELD_MAL_ADRSULN         0,60         0,94         17         24         10         88         26           5         A         HELD_MAL_ADRSULN         0,60         1,43         17         19         15         17         11         17         <td< th=""><th>  A   Q   HELD_MAL_ADRSUIN   Q,54   2,8   11   5   60   106   14     A   C   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   17   24   10   58   80   35     A   C   HELD_MAL_ADRSUIN   Q,60   Q,41   17   24   10   58   80   35     T   C   HELD_MAL_ADRSUIN   Q,60   1,43   17   19   15   17   19   15     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   17   17   17   129   212   46      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADR   Q,60   1,18   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   57   57   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   Q,60</th></td<></th></t<></th></th>	A   G   HELD_MAL_ADRSULN   0,36   2,8   8   11   5   60   106   14     A   G   HELD_ALL_ADR   0,71   1,97   16   24   8   60   106   14     A   T   HELD_ALL_ADR   0,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADR   0,71   1,41   62   98   26   55   99   11     T   C   HELD_MAL_ADR   0,71   1,71   22   12   71   115   27     T   C   HELD_MAL_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAL_ADRSULN   1,06   0,94   17   24   10   58   80   36     A   C   HELD_MAL_ADRSULN   0,7   1,43   17   19   15   70   93   47     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,68   1,46   17   25   9   59   57   21     T   C   HELD_MAL_ADRSULN   0,99   1,27   9   77   77   77   77   77   77   7	A   G   HELD_MAL_ADRSULN   Q,51   1,97   16   24   8   11   5   60   106   14     A   T   HELD_ALL_ADR   Q,79   1,26   132   217   47   131   232   30     A   T   HELD_MAL_ADR   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_FAM_ADRSULN   Q,52   1,92   17   22   12   71   115   27     T   C   HELD_MAL_ADR   1,07   Q,94   62   94   30   60   88   32     A   C   HELD_FEM_ADRSULN   Q,64   1,7   24   10   58   80   36     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,8   1,46   17   25   9   59   59   51     T   C   HELD_MAL_ADRSULN   Q,9   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   17   129   212   46     T   C   HELD_MAL_ADRSULN   Q,99   1,01   47   77   77   78   79   97   21	0         A         Q         HELD_MAL_ADRSULN         0,51         1,87         16         24         8         11         5         60         106         14           9         A         G         HELD_MAL_ADRSULN         0,51         1,97         16         24         8         60         106         14           1         A         G         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADRSULN         0,72         1,72         17         22         12         71         115         27         17         14         24         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,72         1,93         17         19         15         70         99	A         G         HELD_MAL_ADRSUIN         0,36         2,8         8         11         5         60         106         14           A         G         HELD_MAL_ADRSUIN         0,51         1,97         16         24         8         60         106         14           A         G         HELD_MAL_ADRSUIN         0,71         1,41         62         98         26         55         99         11           A         T         HELD_MAL_ADRSUIN         0,71         1,41         62         98         26         55         99         11           T         A         T         HELD_FEM_ADRSUIN         0,72         1,72         17         22         12         71         115         27           T         C         HELD_MAL_ADRSUIN         0,52         1,72         17         22         12         71         115         27           A         C         HELD_MAL_ADRSUIN         0,52         1,72         17         24         10         58         80         36           A         C         HELD_MAL_ADRSUIN         0,71         1,43         17         24         10         58         36         46<	A   O   HELD_MAI_ADRSULN   0,36   2,8   8   11   5   60   106   14     A   O   HELD_MAI_ADRSULN   0,51   1,97   16   24   8   60   106   14     A   T   HELD_MAI_ADRSULN   0,71   1,41   62   98   26   55   99   11     A   T   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     T   C   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAI_ADRSULN   0,52   1,92   17   22   12   71   115   27     A   C   HELD_MAI_ADRSULN   0,60   0,94   17   24   16   15   16   36   36   36     G   A   HELD_MAI_ADRSULN   0,70   1,43   17   19   15   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,43   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,47   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,47   17   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,70   1,71   17   17   129   212   46     T   C   HELD_MAI_ADRSULN   0,70   1,71   17   17   17   17   17   17	A         G         HELD_MAL_ADRSULN         0,26         2,8         8         11         5         60         106         14           A         G         HELD_MAL_ADRSULN         0,79         1,26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         36         69         11           1         A         T         HELD_MAL_ADR         0,92         1,7         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         0,7         1,43         17         24         10         88         26 <th>A         G         HELD_MAL_ADRSULN         0,26         2,8         8         11         5         60         106         14           9         A         G         HELD_MAL_ADRSULN         0,79         1,56         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_FEM_ADRSULN         0,72         1,72         17         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         1,03         62         94         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,71         1,43         17         24         76         <t< th=""><th>A         Q         HELD_MAL_ADRSULN         0.36         2.8         8         11         5         60         106         14           0         A         G         HELD_MAL_ADRSULN         0.79         1.26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0.71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         88         32           1         A         T         HELD_MAL_ADRSULN         0,54         17         24         10         88         32           4         C         HELD_MAL_ADRSULN         0,60         0,94         17         24         10         88         26           5         A         HELD_MAL_ADRSULN         0,60         1,43         17         19         15         17         11         17         <td< th=""><th>  A   Q   HELD_MAL_ADRSUIN   Q,54   2,8   11   5   60   106   14     A   C   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   17   24   10   58   80   35     A   C   HELD_MAL_ADRSUIN   Q,60   Q,41   17   24   10   58   80   35     T   C   HELD_MAL_ADRSUIN   Q,60   1,43   17   19   15   17   19   15     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   17   17   17   129   212   46      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADR   Q,60   1,18   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   57   57   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   Q,60</th></td<></th></t<></th>	A         G         HELD_MAL_ADRSULN         0,26         2,8         8         11         5         60         106         14           9         A         G         HELD_MAL_ADRSULN         0,79         1,56         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         55         99         11           1         A         T         HELD_FEM_ADRSULN         0,72         1,72         17         22         12         71         115         27           A         C         HELD_MAL_ADRSULN         1,03         62         94         30         60         88         32           A         C         HELD_MAL_ADRSULN         0,71         1,43         17         24         76 <t< th=""><th>A         Q         HELD_MAL_ADRSULN         0.36         2.8         8         11         5         60         106         14           0         A         G         HELD_MAL_ADRSULN         0.79         1.26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0.71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         88         32           1         A         T         HELD_MAL_ADRSULN         0,54         17         24         10         88         32           4         C         HELD_MAL_ADRSULN         0,60         0,94         17         24         10         88         26           5         A         HELD_MAL_ADRSULN         0,60         1,43         17         19         15         17         11         17         <td< th=""><th>  A   Q   HELD_MAL_ADRSUIN   Q,54   2,8   11   5   60   106   14     A   C   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   17   24   10   58   80   35     A   C   HELD_MAL_ADRSUIN   Q,60   Q,41   17   24   10   58   80   35     T   C   HELD_MAL_ADRSUIN   Q,60   1,43   17   19   15   17   19   15     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   17   17   17   129   212   46      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADR   Q,60   1,18   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   57   57   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   Q,60</th></td<></th></t<>	A         Q         HELD_MAL_ADRSULN         0.36         2.8         8         11         5         60         106         14           0         A         G         HELD_MAL_ADRSULN         0.79         1.26         132         217         47         131         232         30           1         A         T         HELD_MAL_ADR         0.71         1,41         62         98         26         55         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         53         99         11           1         A         T         HELD_MAL_ADR         0,71         1,41         62         98         26         88         32           1         A         T         HELD_MAL_ADRSULN         0,54         17         24         10         88         32           4         C         HELD_MAL_ADRSULN         0,60         0,94         17         24         10         88         26           5         A         HELD_MAL_ADRSULN         0,60         1,43         17         19         15         17         11         17 <td< th=""><th>  A   Q   HELD_MAL_ADRSUIN   Q,54   2,8   11   5   60   106   14     A   C   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   17   24   10   58   80   35     A   C   HELD_MAL_ADRSUIN   Q,60   Q,41   17   24   10   58   80   35     T   C   HELD_MAL_ADRSUIN   Q,60   1,43   17   19   15   17   19   15     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   17   17   17   129   212   46      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADR   Q,60   1,18   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   57   57   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   Q,60</th></td<>	A   Q   HELD_MAL_ADRSUIN   Q,54   2,8   11   5   60   106   14     A   C   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_MAL_ADRSUIN   Q,71   1,41   62   98   26   55   99   11     A   T   HELD_FEM_VEFF   Q,82   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   151   234   68   144   243   45     T   C   HELD_MAL_ADRSUIN   Q,52   1,23   17   24   10   58   80   35     A   C   HELD_MAL_ADRSUIN   Q,60   Q,41   17   24   10   58   80   35     T   C   HELD_MAL_ADRSUIN   Q,60   1,43   17   19   15   17   19   15     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   25   99   59   50     T   C   HELD_MAL_ADRSUIN   Q,60   1,46   17   17   17   17   129   212   46      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      T   C   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   99   59   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90   50      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   16   23   95   71   90      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,48   187   109   139   178   100      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADRSUIN   Q,60   1,18   05   35   55   64   14      G   A   HELD_MAL_ADR   Q,60   1,18   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   57   57   55   55      G   A   HELD_MAL_ADR   Q,60   1,18   05   05   55   55   55   55      G   A   HELD_MAL_ADR   Q,60   Q,60

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	· <b>L1</b>	26	76	14	41	28	95.	0%	40	727	99	34	17	81	38	121	PL.	٠ ٦٨	· 39	68	0/	42
SIZE HITTEOLED	E11	. 112	112	94	109	112	404	964	. 72	. 340	. 482	236	121	151	72	449	154	154	7.5	. 27	156	76
SIZER	59	69	69	54	1/1	70	230	283	99	281	273	135	69	911	55	285	114	114	57	57	113	53
RREOT X	. 23	18	38	16	19	15	75	84	9	181	83	. 40	22	. 41	14	06	41	32	==	.23	. 103	99 .
	73	36	8	0	. 473	123	405	452	12	190	445	234	<b>2</b>	53	18	454	æ	58	21	3.5	133	. 89
<b>和图图等</b>	48	27	64	20	267	69	240	268	6	1/2	797	137	53	47	16	272	24	54	16	29.	811	19
THE	1,47	89,	1,33	n I	1,23	0,67	1,14	1,14	16'0	0,87	1,18	1,09	1,38	1,29	1,35	0,85	0,88	=	10,1	1,17.	1,29	1,29
	89'0	0,59	0,75	0	18'0	1,5	0,87	0,87	1,	1,15	0,85	0,92	0,73	11/0	0,74	81,1	1,14	16'0	0,99	0,86.	0,77.	0,77
COMPARISON	HELD FEM UBFF	HELD FEM ADRIULN	HELD_FEM_ADR	HELD_MAL_ADRSULN	HELD FEM EFF	HELD_FEM_ADR	HELD_FEM_EFF	HELD_FEM_EFF	HELD_MAL_ADRSULN	HELD FEM BFF	HELD_FEM_EFF	HELD FEM VEFF	HELD FEM DEFF	HELD_ALL_ADR3ULN	HELD_MAL_ADR3ULN	HBLD_FEM_EFF	HELD_ALL_ADRSULN	HELD_ALL_ADR3ULN	HELD_FEM_ADRSULN	HELD FEM ADROULN	HELD_ALL_ADR	HELD_FEM_ADR
ALCE GR	¥	၁	ပ	4	Т	ပ	ပ	၁	£-	T	T	F	H	Ð	ۍ 	<b>o</b>	F	H	Т	F	F	H
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	13479	13633	13633	13929	14065.	14083	14085	14087	14102	14102	14103	14103	14103	14129	14129	14326	14503	14503	14503	14503	14537	14537

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INTERIOR IN		P	त्र	54	7	· L	9	9		7/	£	13	. 40	72	2 2	\$	<u> </u>	6		.	<b>ə</b>	.7.	52	13	:	2	25
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SZE	***	3.	3 3	<u>s</u>	18	9	34	25	1	5	S E	7	<b>S</b>	129	9	<b>3</b> .	28	18	9	Ş	3	31	280	47	70	3 2	Š
THE OF	31.	5 5	3	2	4	15	=	0	105	£   5	3 2	ν,	15	20	77	; ,	c	1	4	<del> </del>	-	2	38	9	α	,	2
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Y ZIS	63	E	25	3 =	2 5	£	19	15	122	38	183	2	:	56	31	5	3	1.	36	9	1.5	5 6	787	<b>o</b> ,	12	16	
AND MAG	0,94	0,92	0.53	α-	200	2	1,75	0	1,27	1,29	1.54	2	2	1,46	1,53	100		0,18	0,62	8,06	90	2 5	Ca's	7,61	2,04	12	-
	1,07	<u>2,</u>	1.89	95.0	0.77	7/1/2	0,57	Mod	0,79	0,78	0,65	99	-	0,69	0,65	253	-+	2,0	1,62	0,12	76.0		-+	0,38 2	0,49 2	0,67	4
BLBA COMPARISON	HELD_FBM_ADR	HELD_ALL_ADR	HELD_ALL_ADR3UEN	HELD MAL CC	HELD ATT CC	The Paris .	neld_MAL_LIP	HELD_MAL_ADRIULN	HELD_ALL_ADR	HELD FEM ADR	HELD FEM UEFF	HELD FEM ADRILLN	_	HELD ALL ADRSULN	HELD FEM ADRIULN	CVD ALL		WEN CIO	CVD_MAL	HELD_MAL_ADRSULN	CVD ALL	臣	-	ADKOULN TEN ADKOULN (	HELD_ALL_ADRSULN   0	HBLD_MAL_ADRIULN 0	-
WELDIE.	<b>ပ</b>	၁	S	A	K		;	9	¥	¥	T	9	U	,	<sub>v</sub>	K	\ 		V	E-	¥	4	4		<u> </u>	CH	
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3103	CIRCI	15915.	15915	19289	19289	19289	16060	orcar.	37158	37158	37160	37412	37412	21.55	3/412	37457	37457	27457	10410	37.704	38959	38959	39292	20000	76765	39698	

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	37	36	29	. 31	31 ·	96	. 28	. 51	. 36 .	. 58	. 53	22	. 27	15	12	14	99	16	48	43	36	36
	15	72	159	87	87	. 436	. 011	219	82	54	. 28	254	·147	. IT	92	. 86	139	179	.68	93	78	78.
SULFIE	44	54	113	59	65	266	69	135	53	99	69	138	87	43	44	99	119	135	58	89	57	57
WIND A SIZE OF	6	. 26	£7.	47	. 13	. 63	11	34	10	. 45	89	111		0	0	16	- 49	120	7	46 .	. 55	17
V TOBILI	29	78	191	8	15	469	93	244	œ	75	62	297	30	14	91	0	33	152	25	58	63	11
Molecular	61	52	113	53	41	266	. 52	139	6	9	59	154	23	7	∞	· mo	44	136	16	22	<b>S</b> .	27
H	0,54	0,31	1,04	1,23	2,01	9/,'0	0,62	0,76	2,45	0,75	1,33	0,62	0	٥	0.	null	1,51	1,24	0,47	1,35	1,35	1,67
MIL	1,85	1,24	96'0	18'0	2,0	15,1	1,62	1,32	0,41	1,33	0,75	1,62	Ima	Inu.	null.	0	99'0	0,81	2,11	0,74	0,74	9,0
COMPARISON C	HELD_FEM_ADR3ULN	HELD_MAL_ADR	HELD_ALL_ADR	HELD_FEM_ADR	HELD_FEM_ADRSULN	HELD FEM EFF	HELD_FEM_UEFF	HBLD_FBM_VBFF	HELD_MAL_ADRSULN	HELD_MAL_ADR	HELD_FEM_ADR	HELD FEM VEFF	HELD_ALL_ADRSULN	HELD_MAL_ADRSULN	HELD_FEM_ADRSULN	HELD_MAL_ADRSULN	HELD_ALL_ADR3ULN	HELD_FEM_VEFF	HELD_MAL_ADR3ULN	HELD FEM UEFF	HELD_FEM_ADR	HELD FEM ADR3ULN
VEHILLER	ပ	၁	ပ	၁	၁	Ţ.	٢	Ţ	IJ	O	V	Ŀ	9	9	G	၁	C	V.	Y	V	[-4	T
VEGNERA	. <b>L</b>	T.	Т	T	T	Ö	Ð	Ö	Ą	£	ວ	O,	A.	A	<b>V</b> .	[- ·	Ţ	. ט	Ç	၁	၁	C
HAYSWE!	39756	39951	1366È	39951	15668	40466	40466	40466	44442	55504	55542	55670	55736	55736	55736	55748	55813	. 55845	55845	55845	55923	55923

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	6,0	0,58	0,82	1,57	1,77	arg	0,71	0,57	0,84	2,0	0,73	┯-			0,93	0	0	1,86	12.1	2.22	0,66	┵		
	HELD_FEM_ADR	HELD_FEM_ADR3ULN	HELD_ALL_ADR	HBLD_MAL_ADR3ULN	HELD MAL ADRSULN	HELD_ALL_ADRSULN	HELD_REM_URFF	HELD ALL ADRSULN	HELD_ALL_ADR3ULN	HELD FEM ADRSULN	HELD FEM ADRIULN	HELD FEM ADR	HELD FEM ADR3ULN	+	$\neg$	HELD_MAL_ADR3ULN	HELD MAL ADRSULN	HELD_MAL_ADR	HELD FEM EFF	HELD MAL ADRIULN 2	HELD_FEM_ADR3ULN 0	HELD_FEM_ADR3ULN 0	HELD FEM ADR	
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- 162 -

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	94	94	74	274	143 · ·	. 124	143	7,5	32 ·	. [1	9/	<i>L</i> 9	53	265	. 89	135	797	89	57	54	95	145
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	28	96	106	524	285	42	206	76	16	64	65	45	28	457	16	238	451	. 06	29	48	9	195
N. aras	36	201	52	285	154	56	150	25.	57	39	55	25	15	265	52	139	267	22	91	56	17	153
	1,63	1,21	0,52	0,77	12'0	0,47	8	0,97	0,77	0,82	1,26	1,63	0,32	0,79	0,62	0,79	0,86	99'0	0,38	1,29	2,04	16'0
RICE	19'0	0,83	1,91	1,29	1,42	2,13	0,93	1.0	<u>E,</u>	1,23	0,79	190	3,15	1,26	1,62	1,26	1,17	1,52	2,61	0,78	0,49	<u>2</u> ,
COMPANSON CO	HELD_ALL_ADRIULN	HELD_ALL_ADR	HELD_FEM_UEFF	HBLD_FEM_EFF	HELD_FRM_VEFF	HELD_ALL_ADR5ULN	HELD_FEM_VEFF	HELD FEM UEFF	CVD_ALL	CVD_MAL	HELD FEM UEFF	HELD_FEM_ADR3ULN	HELD_MAL_ADR3ULN	HELD FEM EFF	HELD_FEM_UEFF	HELD FEM VEFF	HELD FEM EFF	HELD FEM UEFF	HELD_MAL_ADRIVEN	HELD MAL ADR	HELD MAL ADR3ULN	HELD FEM VEFF
AUTOUR	A	· <b>V</b>	Ü	ပ	ပ	ဗ	T	T	T	T	၁	Ð	D	၁	ပ	ပ	A	A	A	Ð	O	T
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HAWSINE	56780	56780	56876	56876	92895	86978	57000	57000	57000	27000	57313	57734	57837	57853	57853	57853	57854	57854	57854	58295	58402	\$8407

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8	76	2   5	2	8	99	99	123	Ş	777	77	7	7	17	129		ñ	59	59	281	19	5	20	128	85	75	5 5
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	1,23	0,68	0.55	80	3	0,28	0,7	0.47	0.56	. 25	3 8	Ę,	0,38	1110	0	155		3,42	1,17	1,34	-	1	+	69'0	1,53	0,57
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THEO 2. A	58	32	18	25	. 15	6	23	14	35 .	. 15	24	14	π	87	29	57	102	190	48	43	85	36	
TRUGUTA	38 .	20	12	19	21	7	21	12	47	13	. 28	2	10	103	39	47	140	290	52	73	167	\$	
Y ans	48	79	15	77	<b>8</b> 2	80	22 ·	13	4	E.	26	80	16	95	34	22	121	240	20	58	126	99	
	1,53	1,68	2,56	7	0,94	2,51	2,27	2,52	1,55	2,14	1,93	7.7	2,39	1,21	1,21	1,29	-	96'0	1,55	1,07	0,99	0,79	
	99'0	650	65,0	5,0	1,07	4,0	0,44	40	0,64	0,47	0,52	6,13	0,42	0,83	0,83	0,78	-	1,04	0,64	0,94	1,01	1,27	
COMPARISON	HELD_ALL_ADR3ULN	HELD ALL ADRSULN	HELD_MAL_ADR3ULN	HELD_ALL_ADRSULN	CVD_FEM	HELD MAL ADRSULN	HELD ALL ADRSULN	HELD_MAL_ADR3ULN	HELD ALL ADRIULN	HELD FEM ADRSULN	HELD ALL ADRSULN	HELD MAL ADRSULN	HELD MAL ADRITTIN	HELD_ALL_ADR	HELD_ALL_ADR3ULN	HELD FEM ADR	HELD FEM VEFF	HELD FEM EFF	RELD_FEM_UEFF	HELD_MAL_ADR	HELD_ALL_ADR	CVD_MAL	
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	7.4	153	99	87	26	25	7	52	29	73	204	73	198	31	469	241	28	42	511	353	238	178
	99	141	52	55	17	13	7	75	13	55	153	. 55	152	17	152	85	52	E	286	269	119	49
	1,42	1,13	1,18	1,44	. 2	0,75	80,1	2,12	2,36	9,65	0,82	89,0	8,	67,0	6,63	89,0	0,89	1,24	0,78	1,13	0	-
	0,7	0,89	0,85	0,69	0,5	1,32	0,93	0,47	0,42	55,1	1,23	84,	17.	3,44	1,6	1,47	1,12	0,81	1,28	0,88	T	
	HELD_FEM_ADR	HELD_FEM_VEFF	HELD FEM UBFF	HBLD_MAL_ADR	HBLD MAL ADRAULN	HELD_ALL_ADRSULN	HELD MAL ADRSULN	HELD FEM ADRSULN	HELD FEM ADRSULN	HELD FEM UEFF	HELD_FEM_VBFF	HELD FEM UEFF	HELD FEM VEFF	HELD_MAL_LIP	HELD FEM EFF	HELD_FEM_VEFF	HELD_FEM_ADR5ULN	HELD_ALL_ADRSULN	HELD FEM EFF	HELD_FEM_EFF	HELD_ALL_ADR	HELD FEW ADR
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A SIZETH GREGOTH	288	. 68	74	240	73	232	501	34	84	891	91	47	37	11	20	36	58	384	08£	49	57	234
SIZIER	253	98	40	125	39	121	19	77	54	611	99	32	9E .	62	15	31	· 8E	261	274	31	16	126
100	244	23	· 0	0	2 .	0	12	10	63	14	200	21	5	9.	4	12	. 17	• 110	202	48	1 .	.46
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W ms	. 249	29	28	52	30	25	13	30	88	44	78	67	12	73	9	21	20	270	283	69	. 43	23
	1,13	0,83	0	0	0,65	0	1,93	0,84	0,82	0,55	0,47	2,08	0,37	0,5	-	0,69	1,71	0,84	1,112	1,22	0,28	num num
HH!	0,89	1,21	Ilua	Ilm	1,55	1	0,52	1,19	171	1,83	2,12	0,48	2,71	2,02	-	1,44	0,58	1,19	6,0	0,82	3,59	0
SECOMPARISON SE	RELD_FEM_EFF	HELD_FEM_ADR	CVD_FEM	HBLD_ALL_ADRSULN	CVD_FBM	HELD_ALL_ADRSULN	HELD FEM ADRSULN	HELD_FEM_CC	HELD MAL ADR	HELD ALL ADRIULN	HELD FEM ADRIULN	HELD MAL LIP	HELD FEM LIP	HELD FEM ADRAULN	CVD_FBM	CVD_ALL	CVD_FEM	HELD FEM EFF	HELD FEM EFF	CVD_MAL	HELD_FEM_ADR	HELD_ALL_ADRSULN
Antiene	Ą	C.	Ð	Ð	T	F	Q	9	Ð	υ	. D	T	T	T	T	T	J .	Ð	ß	Ð	A	Ą.
Arribrankan	Ď	۳	¥	V	O	O	Α.	A	A	Ę	L	O	O	Ü	υ	U	T	Ü	၁	Ċ	O	0
BAVSNP	900124	900132	900144	900144	900145	900145	900146	900146	900146	900147	900147	961006	961006	961006	961006	961006	900200	900204	9002005	900205	900223	900225

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N 0 null V 5,9 0,17 V 1,39 0,72 V null 0 0,97 1,03 V 0,97 1,03 V 0,97 1,03 V 0 0,11 V 0 0,54	0,17 17 0,72 17 1,68 31 0 0,0 0,21 48		57     104       72     118       72     84       69     125       60     104       275     373       132     220	10 26 60 13
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4 1,39 0,72 4 0,6 1,68 4 null 0 0,97 1,03 0 null 0 mull 0 mull 0 null 1,87 0,54	1,68 31 0 9 9 1,03 276 null 26 0,21 48			60
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1,87 0,54	Inu	+	+	2 01
	0,54 73	136 10	+	S .   36
HBLD_FEM_ADRJULN 3,09 0,32 31	0,32 31	+	+	3 %
HELD_ALL_ADR 1,42 0,7 136	0,7		-	3   \$
HELD MAL ADRSULN 0 null 9	6	+	+	2

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# <u>Claims</u>

An isolated polynucleotide encoded by a phenotype associated (PA) gene; the 1. polynucleotide is selected from the group comprising

SEQ ID 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 10 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 15 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 20 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292 with allelic variation as indicated in the sequences section contained in a functional surrounding like full length cDNA for PA gene polypeptide and with or without the PA gene promoter 25 sequence.

- An expression vector containing one or more of the polynucleotides of claim 1. 2.
- 30 A host cell containing the expression vector of claim 2. 3.

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- 4. A substantially purified PA gene polypeptide encoded by a polynucleotide of claim 1.
- 5. A method for producing a PA gene polypeptide, wherein the method comprises the following steps:
  - a) culturing the host cell of claim 3 under conditions suitable for the expression of the PA gene polypeptide; and
- b) recovering the PA gene polypeptide from the host cell culture.
  - 6. A method for the detection of a polynucleotide of claim 1 or a PA gene polypeptide of claim 4 comprising the steps of:
- contacting a biological sample with a reagent which specifically interacts with the polynucleotide or the PA gene polypeptide.
  - 7. A method of screening for agents which regulate the activity of a PA gene comprising the steps of:
- contacting a test compound with a PA gene polypeptide encoded by any polynucleotide of claim 1; and detecting PA gene activity of the polypeptide, wherein a test compound which increases the PA gene polypeptide activity is identified as a potential therapeutic agent for increasing the activity of the PA gene polypeptide and wherein a test compound which decreases the PA activity of the polypeptide is identified as a potential therapeutic agent for decreasing the activity of the PA gene polypeptide.
  - 8. A reagent that modulates the activity of a PA polypeptide or a polynucleotide wherein said reagent is identified by the method of the claim 7.

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- A pharmaceutical composition, comprising:
   the expression vector of claim 2 or the reagent of claim 8 and a pharmaceutically acceptable carrier.
- 5 10. Use of the reagent according to claim 8 for the preparation of a medicament.
- 11. A method for determining whether a human subject has, or is at risk of developing a cardiovascular disease, comprising determining the identity of nucleotide variations as indicated in the sequences section of SEQ ID 1-292 of the PA gene locus of the subject and where the SNP class of the SNP is "CVD" as can be seen from table 3; whereas a "risk" genotype has a risk ratio of greater than 1 as can be seen from table 6.
- 12. A method for determining a patient's individual response to statin therapy, including drug efficacy and adverse drug reactions, comprising determining the identity of nucleotide variations as indicated in the sequences section of SEQ ID 1-292 of the PA gene locus of the subject and where the SNP class of the SNP is "ADR", "EFF" or both as can be seen from table 3; whereas the probability for such response can be seen from table 6.

- 13. Use of the method according to claim 12 for the preparation of a medicament tailored to suit a patient's individual response to statin therapy.
- 14. A kit for assessing cardiovascular status or statin response, said kit comprising
  - a) sequence determination primers and
  - b) sequence determination reagents,

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wherein said primers are selected from the group comprising primers that hybridize to polymorphic positions in human PA genes according to claim 1; and primers that hybridize immediately adjacent to polymorphic positions in human PA genes according to claim 1.

- 15. A kit as defined in claims 12 detecting a combination of two or more, up to all, polymorphic sites selected from the groups of sequences as defined in claim 1.
- 16. A kit for assessing cardiovascular status or statin response, said kit comprising one or more antibodies specific for a polymorphic position defined in claim 1 within the human PA gene polypeptides and combinations of any of the foregoing.

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Single Nucleotide Polymorphisms as Predictive Diagnostics for Adverse Drug Reactions (ADR) and Drug Efficacy

The invention provides diagnostic methods and kits including oligo and/or polynucleotides or derivatives, including as well antibodies determining whether a human subject is at risk of getting adverse drug reaction after statin therapy or whether the human subject is a high or low responder or a good a or bad metabolizer of statins. The invention provides further diagnostic methods and kits including antibodies determining whether a human subject is at risk for a cardiovascular disease. Still further the invention provides polymorphic sequences and other genes.

### SEQUENCE LISTING

<110> Bayer AG

<120>

<130>

<160> 292

<170> PatentIn version 3.1

<210>

<211> 1001

<212> DNA

<213> Homo Sapiens

<220>

<221> variation

<222> (501) .. (501)

<223> baySNP 29, ASO1G

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120 180

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  dadeccede eradecreer redecreer decretered derecreed decreered decreered control decreered decreased decrea
                                                                                                                                                                                                                                                                                                      120
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  gggccacccc cgcaccaget gcccacacct gaggacccas taacaatggc cccatcaggg
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tgecetggge gtteagteet tecagecega egcaggetta tecagggtga tggteeceag
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                                                                                                                                                                                                                                                                                                     480
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gggaggeeea gtggggtgae accageacat ggaggtteta tgaetgegge ageegetetg agaeggtgee tggtgeeaee ateateceea eccaceeeg ccaagteetg tgeeteeagt
                                                                                                                                                                                                                                                                                                   660
                                                                                                                                                                                                                                                                                                  720
coccetace cacetacac cocatcagts greatectes catetatas greatetect.
                                                                                                                                                                                                                                                                                                   780
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                                                                                                                                                                                                                                                                                                   900
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gtatcataaa aacagggctg ggtggggagt ccattgtgct catcgtteet actaaagggt acagaaaacc agccccgatg ytggcatgga tgttgcgaat gggcagaatg aatcctgtag
                                                                                   480
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ggagatteec aaagcoctgo titgtgtaga ottoagottt gtgttgagot tigaggagta
                                                                                   660
atteaatett eteteteea tagatettet etecaateat ceteatteta teeteaaete eegagettegag eteataaage agttegaage teetegete tteteeteet etetegaacag
                                                                                  720
                                                                                   780
cctgagccag ggctaaggta cccttgcccc cttctgccag tgagtgcact tcacggcatc
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aaaagccctc tottetetog aaaggcagee gatgaggtee ageteagtet etgtatetgt
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                                                                                  300
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gragaatgee gtetgeaact tgegeattte geagetgeea tettgeeget geteettete
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taggtgttca tegagaaggg macattooto tecacotcag agetggtggg ggaaggcoca
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cecagataay atctytyacc agatcaytya gyctytcott gatgeccace ttcaacaaaa teetyatyce aaaytayett ytyaaactyt tyctaaaact yyaatyatec ttettycacy
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tgaaattaca tecagagetg etgttgaeta acagaaaatg ettegtgaag etattaaaca
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                                                                                  B40
cattggtgtt ggagaccagg gettgatgtt tggetacgcc actgatgaaa etgaggagtg
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                                                                                 180
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                                                                                 360
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                                                                                 480
  540
                                                                                 600
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                                                                                 720
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tageteggag gtegtggege tgggggetag caccageget etgtegggag gegeageggt
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                                                                       560
acadtodaco coccococo cotcococo acaettere recaetter adacadostere
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                                                                       180
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420
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geceteteaa ageceacaca meegeetgee tggggtaaca gtateteete ggacateetg
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teetetgtga gaattteaca coetagtgtg aagteatage ettgtaaett teeetttaag
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attetetggg etgeteggte gatgeetgtg ceaetgaegt ceaggeatga ggtggtteet
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   gtgtaaatat tttaaatgat ctgtaccagg aaagagtcca aagaactagt gggactcctg
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  acaaatteta atteagagte tgattetaga aaacacetea gaaagetaga gteeacactg
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  cectgggcaa tgaaaaagtt yttatgettg tttgaatggg atgggtgtgt Etttggtgte
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  600
                                                                              660
                                                                              720
                                                                             780
                                                                             840
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                                                                           480
                                                                           540
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tatatttttt tattatcat citatatctg titattett ttataaaget getgttaaac
                                                                           560
aatataatta aactatctca aaaggtttga cattaaagaa aatgagcaat ggtaacagga
                                                                           720
aaccactota tagatgtaca tataatatgt acagaaaata taagtagtaa gaagtccatg
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                                                                                240
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                                                                                BOE
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                                                                                360
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720
                                                                                                                                                                                                                                                                                                                                                         780
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Sadactacto factacco decedate decedate establicate des de la contra del contra de la contra del la contra de la contra del la contra del la contra de la contra de la contra de la contra del la contra del la contra de  la 
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- 17

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5.19

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- 21

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- 24

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5.28

- 27 -

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cacaaaatya gygtgagtag g <210> 48	ttottaaatt	tgacatcago	ttgttcaggt	tttcctaaga <sub>.</sub>	780 781	
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-tctgccgttc_ctcaactcaa_ gacagacctg tctctgaaca	ctcaatgcct_	tcctggctta	cttagatetg	ccttggaagg	180	
tccaatcaag tttgtttttt agtggtaggt gggtatttta	ccatttcatg	caggtgtatt	gggctgatgt '	atctatgaca """	240 300 360	

- 30 -

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                                                                                                420
                                                                                                480
                                                                                                540
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                                                                                                600
                                                                                                660
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                                                                                                780
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                                                                                      120
                                                                                      180
aaattagaga cegeteatta tagaettget agttagaagt tatgeatgtt ggacagttga
                                                                                      300
ttgactettt agaaacagta taggtaaagg ggaagactgt ggettttaa ttatacatge ccagacteca acgttggete taccacttat ttcaaagggo tgtaaatatt gagacatgge
                                                                                      420
acggttcctg gcccatagta mgaactaaac aagtgtttta gaattatggt tgtcattacc
                                                                                      480
attgttgtcc atcttactaa ataatgggta taaagttgaa caagctaata acatcagagt
                                                                                      540.
acceactyta aggatytaca antaatttat tttyttyatt tanaanaatc acatttatco
wacactanag tagaaccaat cotcotttat gtotaattgt anatotottg atatottata
                                                                                     56Q
ategacttee atattttace ttttaataat attaggetea gegeacacet gtacagatga
                                                                                     720
tgtacttgcg tgamaagetm aacattggat acatagaaga cctamagget cagattctag
                                                                                     780
aactcccata tgctggagat gttagcatgt tottgttgct tocagatgaa attgccgatg
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                                                                                          120
ggttetetag ageaacagea ataccegece ggeaggggtg tggettagag eccegeacet
                                                                                          180
cottegeograf eggegggeet gaettetage caegggtete egeagttgge ceagegette
                                                                                          240
                                                                                          300
gggeeggtgt teaegetgta egtgggeteg eagegeatgg tggtgatgea eggetacaag
geggtgaagg aagegetget ggaotacaag gacgagttet cgggcagagg cgacctcccc gegttccatg cgcacaggga caggggtgag tecgcgtccc tggcacggag cggggggtgc
                                                                                          360
                                                                                          420
ataacacgcc ccgggacagt tacgggegot agceacgteg gegatggeea aataataaac
                                                                                          480
taacagtaat attatagtaa yagcatccga aggatgagat caggattagg gcgatggccc
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cegegegttg cetgesgage gaggegeact gagtegeeca ggaateegge eteteggega etgtgeggga gagtttatgg ggatgggegg ggetgettet gageaggagt egeegeece acceccaceg tteegeetet gggeegeact gagtegetet egeegeece
                                                                                          600
                                                                                          660.
                                                                                          720
teaaccgccg gggtacaggt ggcttcgtcc accgaggtcc cctcacccac gctgaggcgt cggaagctgc ggacactgct cgcttcaggg ctttgctcag ctgcagctgg tgacctccag
                                                                                          780
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eccaetgasa tectatetee eageeteace tetgetgtet cetecaeget teetgtetee
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                                                                                         120
ctggtaccgt tecttgtect accgtetatg ttgatattaa aaatatcaag agtetgaaac tttacatcat agtgaacaaa gaaaacctaa tatgatgcca gggaaaagat ttcaggatgt
                                                                                         180
                                                                                         240
transatotg ttootgataa aaataatotg aattranaaa totttoatga otgatttta
                                                                                         300
ateacactga ggcaaatate ceceteagae agaggetgea ceggtacage tgecatetee
                                                                                         360
tettggtggt steetttste aagageatst cassstsats asteatetss sacassteat ceteccasea eegagaagee gaesggggas saacasate etetseatts tsateeaatt stsaacaaaa asteetette rtssaacass aaaaatacae teeetetaaa caatssatts
                                                                                         42 D
                                                                                         480
                                                                                         54D
aacacagatg tgatttetaa agaagactga aggeagggat aetgacaetg aagteetgee
                                                                                         600
tytytaataa caccyaagay gycayyyaat cyctycytco tytyacttya agyccactyt
                                                                                         660
gaaggaaaac aatgcagtga aagaaagtto otootatgtg gacattgtat cacgtttatt
                                                                                         720
tatettoetg gatatgotta tggcotttaa aacatattaa aataggetat getattatet ...
                                                                                         780
cttaaaatat ctgttttccc tcaggtaact ggagacgcac cctgctactc ctcacgtcac
                                                                                         840
tettettece taaaccagge tyggootocc actegoocca caggoaggtg acqtatqaca
                                                                                         900
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                                                                                                       60
                                                                                                    120
                                                                                                     180
   aactgaagaa gettaaaaca ggeettaaaa ageaettget gtgteeaage tgeaaaactg etgtgteage tetgaetett eeeettetee tteecetggg tetggggeag ggtggtteaa
                                                                                                     240
                                                                                                     3.00
   geetgtaate ecageaettt gggaggeeaa ggeaggaega teaettgage ecaggaggtt
                                                                                                     360
  gagaccagce taagcaacat agggagacce cecaagtete tetagaataa gaggatgage
                                                                                                     420
  teagaceagg gaaggggtgg yactgggggg acgteacage caggeceace aagtgteatg
tetgaceaca cetgggatte ttaaatatag atgtatttt tteateteat eteeggacae
                                                                                                     480
                                                                                                     540
  actocaatca caccoctyct goodtocoot otcaactgoa aaccaagogg tgcagacaca.
                                                                                                     600
  geacageaca catgaggge cetecettte accasagetg aaggeaggge acagtttggg
                                                                                                     660
  gatggaagag cetegaggta aatgtgggeg ttetagaace cagtgacete agttetggat
catgggaaag ggatcagtat gcagtaacgt ggtaaggtte cagatetaga agecaggace
                                                                                                     720
                                                                                                    760
  tagaacctag tggtttcaca gtgggcagag cagttgggaa taagccaggt taggggtggg
                                                                                                    840
  ggaagacage cagetetgte etetgeagge ggattecetg gagggagate teagatttag
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                                                                                                    60
                                                                                                  120
                                                                                                  180
                                                                                                  240
cetgteceta gggettttta gteacatgte catecatgt tteaatgtaa catgeateta
                                                                                                  300
ggcaaggtta acgattaaat ggttgggatg aaaggtcatc ctttacggag aacatcagaa
                                                                                                  360
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 geaactetac tttttgggtg agaaattaca tttatettea tattgactet teteagaete
                                                                                         600
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                                                                                         660
 gigcaatigg tetaaagete aggetittia gaaageataa ticataatat etecagagga
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                                                                                         840
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                                                                                         900
 agatocgtga otgagtottg otgagacatg ttgatgttga aatgataatg ataagttota
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                                                                                        . 60
                                                                                        120
acaggatggc aggtaatgcg ggtggggaat ggggtaggag ggatgggtgc ttctagaatc
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999cgaaggg octaaaggac cgaaaccaaa tgtctactgg ccagattatt atttctgaag
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teageagagg acaactgtgg gteagactga ettaaacagg gatamaaaag tgaamamaa gtagtgacag eetaaatggg tgaagaagee eagattetgg gggemaaatg eettgggtet gtgaaactgg atetettgtt atteattame eageeegatt teetgageaa gatteeaage
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                                                                                        420
                                                                                        480
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                                                                                        540
agecaacaag tacagtagta ecceettate caetggggat atgitetacg acceecagta
                                                                                        600
gatgittgaa accacagati gcaccaaacc ctatattaot giittitcec ccatacatac atacctetta tagittaatt actaaattac ccacagtaag agattaacaa caatgeeegg
                                                                                        660
                                                                                        720
egeagtgget caegtetgta ateceageae tttgggagge tgaggeggge aaateacetg
                                                                                        780
aggicaggag titgagacca gootggocaa aatggggaaa accigiotic acaaaaatto
                                                                                        B40
aaaaataage caggeatggt gacaegtgee tgtaaeeeca getaeteggg aggetgagge
aggagaatea cetgaaeetg ggaggtggag gttgeagtga getgagatea egecaetget
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Homo Sapiens

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 teagacgeea acttgaacaa etteageete tgttceacet gagtgacaaa aggtgggaag
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                                                                                                                360
                                                                                                                420
ygtgagtcac cgcgcccggt stgacagcét ttccagaatg aagtttgtct cggaaaaaag
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agecetggee agtgteteet etggggatea geggaaagea cetgeacget etggggatea
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                                                                                                                600
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atggaaatga actgatgaca cttctcagga ccactgctaa gaaaatttaa aggacaatgt
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                                                                                                                780
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240 . 300

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                                                                                       120
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                                                                                       300
                                                                                       360
acadastroc adadasasta cercaccasa deraccacca dadasocrata rabadasasta
                                                                                       420
                                                                                       480
                                                                                       540
atcagoggta agtcagonac atgcacoggo tgcagogggg cocatococg cotgggggtc
600
                                                                                       660
                                                                                       720
                                                                                       780
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ggetggeagg geaggteeet aaacaesece aagggeactt cetteacett cecaeteagg etteteagge teeaaggggt tgggggteet ttetagetee ageatteate accceaaage
                                                                                       640
                                                                                       900
agttamacca ttttccatca atcagaagga aaacttgctt ctggaagaca gcaccgtgta
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                                                                                       120
                                                                                       180
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tagtcattgs: tedgacectg tetggacectg tetggacectg tetagetece tetagetece tetagetece tetagetece tetagetece tetagetece tagtcattgs:	tgagtgggaa gtgggtgggg tgcagcactg gtttatggag cccctccctc ttaaggctgc cagagaaggg actcctaggt caaagacatt	gggccaaage yggggggggc aatagctgt gggccaaage	tgctctgttg taccttctty gcccgtgcc tgaccacgcc tctcttccta ttggccagat atggggagtc ctaggctcac	ctgageagtg ctgagagetg ccagargecg agkttgtaga tctgggeege ccacgacatg tgttcccct ctgtgscatc	cagageageg ceaggtacee ggtggggtga tetecatare tetggeeeac tetgeetgga acaetgttet gatgtaatee gaeteteett etetgtgtma gaggtggaga	360 420 480 540 600 720 780 840 960 1001
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                                                                                                                       180.
                                                                                                                      240
gestettee tiggteet ytggtgget gtaggattat cateteeas taggatett ctgacaget tgggateet gtattget gtaggateat cetaggett gtaggateat gtettggt acagtatet gteatacae kteaagagea agaataagae catatacate tteateect gtattacaa atttggtatt tagtaaatgt catatacate tteateectg
                                                                                                                      300
                                                                                                                      3 5.0
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                                                                                                                     78 D
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                                                                                       300 -
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                                                                                      56Ö
                                                                                      720
                                                                                      78 Ó
  attettgtaa aattaatgaa octotoatta toaagagggt ctacattate Egttetacac
                                                                                      B4.0
  tgggttattt taataaaata tttaaaatga tgatctccat catttttgct gctatgtggg
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                                                                                     60
getteettgg categtetag taacacccaa cacagtetgt agettteage tgacacteag
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1001

#### Le A 36 562

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                                                                                   360
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                                                                                   420
cccacagag cagegeaggg gaagaggegg tteagggeea agetgtgeae egaggaggge
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                                                                                   840
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                                                                                                   660
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                                                                              720
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Empfansszeit 31. Jan. 14:08

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Le A 36 562

- 81 -

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TILLY TO LEVERKUSEN

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er annes Alleren.

442 CT4 JA7T024

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1

THE LEVERKUSEN

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BHYER AG LEVERKUSEN

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TER HU. LEVERKUSEN

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S.35

- 138

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BHYER AG LEVERALSEN .

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